THE VITAMINS IN MEDICAL PRACTICE



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PREFACE

AS THE title indicates this work is essentially concerned with the study of vitamins in their application to medical practice. The difficulties of the practising physician in this field are not lessened by the fact that a small proportion only of the massive literature on the subject appears in journals devoted purely to clinical medicine. In the selection of material, the influencing factor has been that it should definitely relate to the physiological and pathological processes of the body. A primary consideration has been that the subject should be covered as concisely as possible without sacrificing essential material It is hoped that, in its sphere, the book will satisfy the needs of the practising physician and prove helpful to those reading for higher medical examinations.

In design the book falls into three parts. Following an introductory chapter, the first part comprises a description of the individual vitamins The second is concerned with the accepted major clinical syndromes referable to body depletion of one or more of the vitamins Finally, the individual systems are considered in relation to the vitamin status of the body, and the value of vitamins in affections which are not attributable to their deficiency is carefully assessed. The problems peculiar to pregnancy, infancy and childhood are dealt with in this section.

The material has been culled from an extensive survey of the literature; the author acknowledges his indebtedness to the existing published works on vitamins A debt of gratitude for most valuable assistance is due to Professor Arnold Sorsby, Mr. W. Price, Dr. A. Markson, Miss C M. Wood and Dr. W. S Cormack; and particular thanks are tendered to Mr Julian J Shafar. The help and co-operation of the publishers are deeply appreciated.

CONTENTS

diagnosis. Minor degrees present a clinical problem; their manifestations are not characteristic of any specific syndrome and usually take the form of general lassitude, fatigability, diminished appetite and, in children, impairment of growth. Some subjects, although presenting a semblance of health, live in the 'twilight zone of nutrition' with no factor of safety, and when pregnancy or illness supervenes an overt deficiency syndrome is made apparent [2].

In general, nutritional deficiency may originate either in the primary form, occasioned by an inadequate dietary, or, in the secondary or conditioned form, in which there is some other abnormal condition responsible for or precipitating the malnutrition. Inadequate intake may arise from economic factors; ignorance of the elements of nutrition, food fads, racial customs, anorexia and mental derangement are among the other causes of primary malnutrition. Consumption of nutritionally inferior foods may have a similar effect and these include highly milled grain products, alcohol and sweetmeats.

Conditioned malnutrition is reviewed by Jolliffe [3]. It is produced by interference with ingestion, absorption or utilization of the vitamins or by factors which increase their requirements, destruction or excretion. The interpretation and correction of these conditioning agencies is as essential as the treatment of the vitamin-deficiency state. Gastro-intestinal disorders, including gall-bladder disease, may diminish the ingestion of food as may the loss of appetite associated with febrile illness, congestive cardiac failure, pregnancy and post-operative states. Therapeutic restrictions of diet should be such as to ensure an adequate supply of the vitamins, for deficiency disorders have followed ill-balanced diets prescribed for peptic ulcer, renal disease, allergy, colitis, diabetes mellitus and obesity. The voluntary reduction of food intake in an attempt to reduce weight is not commonly associated with vitamin deficiency since the low caloric content of the diet affords some measure of protection; if persisted with, however, serious effects may ensue. Under certain circumstances an increased vitamin requirement arises. Fever, hyperthyroidism, pregnancy and lactation, abnormal degrees of activity and therapeutic measures such as thyroid and dinitrophenol administration, artificially induced fever and high carbohydrate diets may be mentioned as examples. Defects of absorption may be associated with achlorhydria, obstructive jaundice and disease of the alimentary tract. Jolliffe also draws attention to the adverse effects of severe catharsis, and also of certain medicaments, such as liquid paraffin and colloidal adsorbents. Factors interfering with utilization are present in hepatic disease, hypothyroidism, malignancy and the use of sulphonamide drugs. Polyuria and lactation may account for increased excretion of vitamins and there also

remains the possibility of increased destruction of vitamins in the body necessitating an increased intake.

The rate of development of the signs and symptoms of vitamin deficiencies will depend on the amount of prenatal stores present in the infant (reflected in the maternal dietary) and, in the later stages of life, on the body reserves of vitamins prior to the commencement of the faulty dietary regime. Vitamins A, E and K are readily stored while vitamins B_1, C, D and riboflavin can be retained in the tissues in only moderate amounts. It is almost axiomatic that if human dietaries are deficient in one factor they are likely to be deficient in many.

Growth is a condition meriting special attention and nutritional defects in children tend to appear or to be accentuated at three periods – infancy, second dentition and puberty – when the nutritional needs are at their greatest. The metabolic level greatly influences the development of signs of a deficiency state, for even in the presence of a markedly deficient intake no effects may be evident while the patient is confined to bed.

. The detection of nutritional deficiency is obtained from a study of the dietary habits, the medical history, the physical examination and from special methods of investigation. Vitamins are primarily created in vegetable sources and thence appear in animal tissues. Reduction of vitamin content from the original level arises from the several processes to which the foodstuff is subjected prior to its ingestion by man Harvesting, transport, storage and cooking will all tend to lower the quantity of vitamins contained. The amount of vitamin present in the consumed article does not represent that made available to the body for loss from excretion and non-absorption must also be taken into consideration. Hence assessment of the value of a diet in respect of its vitamin adequacy must take account of all possible losses. The distinction between a satisfactory and a poor diet is largely referable to the quantities of milk, lean meat, fresh vegetables and fruit included.

As in all clinical examinations a careful and detailed medical history is of paramount importance. The possibility of a bodily disorder as the conditioning cause of a nutritional defect must be investigated. The clinical signs may accordingly represent a combination of those attributable to the primary disease and those occasioned by the lack of vitamins. Spies [4] lists the following symptoms as suggestive of a possible vitamin deficiency state: loss of weight and strength, headaches, dizziness, burning sensations in the skin, roughness and dryness of [illegible]
of vision, lachrymation, photo [illegible]
cramping of the stomach, bur [illegible]
and ulceration of the oral and lingual mucous membranes, saliva-

tion, diarrhoea, burning and cramping of the feet, insomnia, nervousness, loss of memory and emotionalism. In children an appraisal of the general nutrition is made and attention is directed to some special points in the physical examination. The head should be palpated for evidence of delay in closure of the anterior fontanelle, craniotabes and parietal bossing; cracks, sores or scars at the angles of the mouth, and gingival changes and bleeding should be sought as should signs of glossitis. Examination of the teeth, with regard to date of eruption and the existence of any abnormalities is indicated and the presence of dermal changes around the nares, forehead and eyes is determined. The eyes may offer important information and if necessary slit-lamp microscopy should be adopted. Other bony changes of rickets may exist in the form of enlarged epiphyses, beading of the ribs, thoracic deformities and genu valgum or varum. The skin is examined for abnormalities of the follicles ('toad skin') especially at the medial sides of the thighs and for any evidence of haemorrhage. Changes in the condition of the hair are also important. In adults the examination of the tongue and mouth, the nasolabial folds and the eyes is conducted as in children. Follicular hyperkeratosis and other skin lesions are looked for, including a bilateral symmetrical dermatitis, pigmentation, thickening and darkening of the skin, purpura, 'Casal's necklace' and dermatitis of the scrotal and vulval areas. Vaginitis may be a manifestation of a deficiency disease. Neurological examination is essential as is the determination of the patient's mental state.

Laboratory methods for assessment of the vitamin status of the body are numerous. Among them are the vitamin concentration of the blood, the excretion of the vitamin or its excretory products in the urine, vitamin 'tolerance tests', biopsy studies and various functional tests such as measurement of dark adaptation, blood phosphatase, blood pyruvic acid and capillary fragility. Specialized tests have their limitations and their interpretation is often difficult. As an example, the value of the blood level of a vitamin has been criticized by Kruse [5] who points out that it shows ready fluctuations and does not necessar [illegible] the ti [illegible] of the vitamin; the blood co[illegible]ntration [illegible] te [illegible] tly while the concentrati [illegible] e tissu [illegible] lo[illegible]

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legislation regarding bread in Great Britain have gone far in improving the protective value of the diet.) In this respect the investigation of Sydenstricker [6] of the nutrition of Britain under wartime conditions produced significant results. After three and a half years of rationing, an examination of 5,000 unselected civilians showed occasional mild folliculitis but no other evidence of vitamin-A deficiency; only one case of mild pellagra was encountered, 8 women had signs of riboflavin deficiency and 38 others had corneal vascularization characteristic of riboflavin deficiency.(Education in fundamental dietary principles should be instituted in schools and in the adult population, and individual idiosyncrasies of diet and faulty racial dietary customs should be overcome. The medical profession can play a most important part in the dissemination of such knowledge. On the other hand the indiscriminate consumption of synthetic vitamin preparations because of their supposed 'tonic' effects is greatly to be deprecated. As McLester [2] so aptly phrases it: 'For the maintenance of health a person should look not to the druggist but to the grocer and the dairyman.' Advances in nutrition of the industrial worker have been made by the institution of proper canteens, but it remains for the nations of the world to act together in the proper distribution of food to all countries [7]. The other aspect which has been stressed already is that of recognizing the possibility of deficiency states developing in the face of increased requirements or conditions detrimental to adequate nutrition. Careful consideration should be paid to the convalescent stage of illness or injury and the nutritional defects accruing from them made good during this period. Vitamins are administered either as supplementary preparations or for therapeutic purposes [8]. The former provide an amount sufficient to ensure an adequate intake and this quantity is supplementary to that supplied by the diet. Therapeutic dosages are larger. Both measures include one or more essential factors and precautions should be taken against the precipitation of a vitamin imbalance from the use of heavy doses of a single vitamin. The question of what constitutes the normal requirements of each vitamin has revealed differences of opinion, some authorities holding that the prevention of ill-health is the basic consideration while others would desire a state of saturation of the tissues with the essential nutrients. Sir John Boyd Orr expressed the physiological ideal as a state of well-being which cannot be improved upon by a change in the diet. Dann and Darby [9] recognize five zones of nutrition – saturation, unsaturated but functionally unimpaired, potential deficiency disease, latent deficiency disease and manifest deficiency disease. Supplementary vitamin administration is exhibited when the diet is unsatisfactory or when an

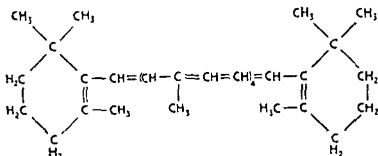
VITAMIN A

VITAMIN A is also known as the anti-xerophthalmic vitamin, axerophthol and the anti-infective vitamin. Xerophthalmia, a manifestation of severe vitamin-A deficiency, presents but one aspect of the deficiency syndrome, and is too limited to serve as a satisfactory designation. Axerophthol is an infrequently used term. The descriptive name 'anti-infective vitamin' originates from a misconception of the properties of the vitamin in relation to infective processes; it should no longer be employed as a synonym for vitamin A. Vitamin A includes vitamin A_1 and vitamin A_2 and the naturally occurring precursors are referred to as provitamins A.

Vitamin A_2. – The features which distinguish vitamin A_2 from vitamin A_1 will be given briefly and in the subsequent discussion vitamin A will be considered to refer to vitamin A_1. There is a difference in distribution, vitamin A_2 predominating in fresh-water fish and vitamin A_1 in salt-water fish. The vitamin A pattern of the species is largely determined by genetic factors. Vitamin A_2 is absent from the livers of mammals unless the vitamin has been present in large supply in the diet. Both vitamins appear to have common precursors since when carotene is fed to fish such as perch both vitamins can be formed [12]. There is still dubiety regarding the exact chemical structure of vitamin A_2. Little significance can be attached to the rôle of vitamin A_2 in the human body although biologically its functions would seem to be the same as those of vitamin A_1.

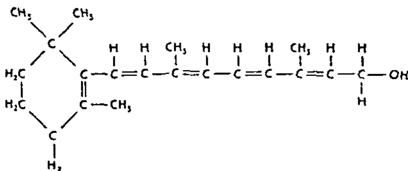
Properties of Vitamin A and its Provitamins. – The carotenoids include vitamin A and a group of plant pigments. The latter possess similar chemical structures and properties and their natural distribution is in association with fats to which they give the distinctive coloration. Certain of the carotenoids, known as the carotenoid pigments, occur widely in the plant kingdom, and carotene is a term employed to include these carotenoid pigments. Carotene is synthesized in plants but vertebrates do not possess this capacity. The function of carotene in plants is not clear but with certain exceptions its concentration in green leaves parallels that of the chlorophyll Some carotenoid pigments can be converted into vitamin A – the vitamin-A-active group – while this property is not present in the members of the vitamin-A-inactive group. Of the former, four are of particular importance, beta-carotene, alpha-carotene, gamma-carotene and cryptoxanthin. Beta-carotene is the most abundant and its activity is about twice as great as that of the alpha- and gamma-derivatives.

Chemically the carotenes are unsaturated hydrocarbons made up of a long aliphatic chain which contains 18 carbons in those compounds capable of conversion to vitamin A. The various provitamins are distinguished from one another by the composition of the groups at the end of the chain. Since the beta-ionine ring is an essential component of vitamin A this offers an explanation of the manner whereby beta-carotene gives rise to two molecules of the vitamin. Both the end groups of beta-carotene are composed of a beta-ionine ring whereas the other provitamins show the latter structure in only one end group and can thus yield but one molecule of the vitamin. The graphic structure of beta-carotene is shown below:



Vitamin A is probably formed by hydrolytic rupture of the middle of the aliphatic chain although recently it has been suggested that oxidation is concerned in the process of conversion. Carotenes are insoluble in water but soluble in fats, and they form esters with fatty acids. They are readily inactivated by oxidation and by light. The naturally occurring provitamins A are found in only small proportions in the free form and exist chiefly in combination with proteins or as esters. Characteristic absorption bands in the visible spectrum are exhibited by the carotenes.

Vitamin A, an unsaturated alcohol, is present in the unsaponifiable portion of certain fish oils and can be obtained in synthetic form. The formula is $C_{20}H_{30}O$ and its structural composition is



Vitamin A is soluble in fats and certain fat solvents and forms esters with fatty acids. The fatty acid esters are more stable than the vitamin which is sensitive to light (hence cod-liver oil is stored in dark-coloured bottles) and to oxidation. Vitamin-A concentrates are composed principally of the esters which are obtained by molecular distillation of the fish oil. The vitamin is heat resistant in the absence of air but is destroyed in the presence of oxygen. In contrast to the reddish-yellow colour of carotene, vitamin A is almost colourless, and with antimony trichloride a green-blue colour is given by the former substance and a deep blue by the vitamin. Within the tissues vitamin A exists both in the free state and as esters. Its occurrence is restricted to the animal kingdom and it has not been recovered from plant life.

Units of Vitamin A

Vitamin A is measured in reference to a standardized preparation of beta-carotene. The international unit is a measure of the vitamin-A activity of 0·6 microgram of this preparation. The United States Pharmacopoeia unit was introduced as of equivalent value, using Reference Cod Liver Oil of the U.S.P. as the standard. From the employment of biological methods the Sherman-Munsell unit has been suggested but has proved of little value. Blue units are referable to the intensity of the blue colour produced with antimony trichloride.

Metabolism and Physiology of Provitamin and Vitamin A

Absorption of carotene and vitamin A proceeds from the alimentary tract through the wall of the duodenum and upper jejunum [13]. Carotene is absorbed as such, while the esters of the vitamin are first hydrolysed and then reappear in the lacteals in the esterified form High fat diets facilitate their absorption but beyond a certain dietary fat content no increase in the absorptive mechanism occurs. In general those factors which affect the absorption of fats also affect the absorption of vitamin A and its provitamins. This influence is portrayed in the condition of steatorrhoea. The presence of bile is of great importance for the absorption of carotene but in its absence vitamin A is readily absorbed, although in a somewhat lesser degree than normal [14, 15]. Mineral oils exert an adverse influence and if consumed over long periods may seriously interfere with vitamin-A nutrition. Carotene is less effectively and more slowly absorbed than vitamin A and following oral administration maximum blood levels of the vitamin are reached before those of carotene [16].

From the lacteals vitamin A and carotene are carried to the thoracic duct. In a case of chylothorax Drummond *et al.* [17]

found that reasonably large quantities of vitamin A were returned almost quantitatively in the chyle although the recovery of carotene was far short of quantitative. Within the intestinal lumen oxidative destruction may take place and the stability of both substances rests on the nature and amount of anti-oxidants available. Of particular importance as protective agents are the tocopherols whereas rancid fats exert profoundly deleterious effects.

Carotene is converted into vitamin A in the body. The chief site for the transformation is the liver, and an enzyme, carotinase, is concerned in the reaction. Incubation of carotene with fresh liver tissue, or with an aqueous extract of liver, promotes the change; the enzyme is inactivated by heat [18]. The work of Sexton *et al* [19] indicates that the intestinal wall may also be a possible site for the conversion of the provitamin. Participation of the thyroid in carotene conversion has been suggested by the change in colour of the milk of thyroidectomized goats from the normal white to yellow, due to the inability of the animals to change carotene to the colourless vitamin A [20]. There is no evidence that the opposite reaction, the reversal of vitamin A to carotene, can take place in the body.

A species difference in the storage depots of vitamin A exists. The liver of rats and rabbits yields about 95 per cent of the total amount present, while in certain varieties of fish the content in the intestinal wall exceeds that of the hepatic stores. In man it has been estimated that the liver holds some 95 per cent of the vitamin A. The fat depots and fat cells scattered throughout the body normally are not rich in the vitamin but in view of their large mass they rank second to the liver in tissue storage of vitamin A [21]. Other sites of storage include the skin, muscles and bones. Popper [21] stated that the normal kidneys contain no vitamin A but that in renal disease its presence was demonstrable. An opposite conclusion was reached by Lawrie *et al.* [22] who considered that it is the healthy kidney that stores the vitamin whereas it disappears from the diseased organ. Little is known of the factors influencing the discharge of vitamin A from the liver into the blood stream. The nervous system would appear to play a considerable rôle in the mechanism, and sympathomimetic drugs, such as adrenaline, effect an elevation of the plasma vitamin-A level [23]. Peculiarly enough alcohol exerts a similar action [24].

Vitamin A and carotene are present in the serum but not in the erythrocytes; the vitamin is transported both in the free and esterified forms of which the much smaller and variable proportion exists as the free alcohol. With normal average nutrition the plasma vitamin-A concentration remains at steady levels during the course of the day and from day to day. The normal value of the plasma

vitamin A is usually given as between 100 and 300 internatio units per c.c. The normal total carotenoid content of blood seri ranges from 50 to 300 micrograms per c.c. but may be much higl [25]. Gross changes in the dietary content of the vitamin or provitamins do not permanently affect the vitamin-A level. A ministration of vitamin A results in an elevation of the plas concentration but after twenty-four hours the original value usually restored; doses as high as 100,000 units did not delay t return [26]. Continued intake of large supplements of the vitan were ineffective in establishing a persistent elevation of the blo vitamin-A level [27]. In addition to nutritional deficiency oth processes are capable of reducing the serum values.

Carotene plasma levels show little fluctuation following average meal. High consumption of carotene, as such or contain in food, produces an increase in the plasma content, the degree a duration depending on the amount ingested and on the stores carotene in the body. As the dose rises there is a proportiona reduction in its effects on the plasma carotene level owing increased loss in the faeces [28]. Large doses of carotene displ their influence on the plasma levels over a considerable period a Ralli *et al.* [29] found that the peak was not reached until sevent two hours after administration following a dose of 600 mg. of car tene in oil and that a slow return to normal figures proceed thereafter for over a week; continued ingestion of carotene reflected in a steady rise in the serum content and there appear to be no limit to the possible elevation which might be reache Associated with the increased carotene serum values there is response of the vitamin-A concentration but this is much le pronounced and much more fleeting. Diets from which a sources of the vitamin are absent effect a fall in the plasma car tene, the vitamin-A concentration being undisturbed until th former is reduced to very low values [30]. Wide variations the carotene serum content are obtained under ordinary conditio and reported figures range between 50 and 420 micrograms pe cent [28]. There is a richer content of carotenoid pigments i the fat deposits of elderly subjects as compared with those younger individuals, a fact which has been offered in explanatio of the lower carotene and higher vitamin-A plasma concentration found in the latter [31].

Intraperitoneal or subcutaneous injection of carotene produce no increase in the hepatic stores of vitamin A in the rat and although capable of remedying the manifestations of the deficienc state, the amount required is 10 to 100 times as great and th effect less prolonged than when the carotene is given orally; only a portion of the carotene in these sites is available to the anima

since deficiency symptoms and death may occur even while considerable quantities of carotene are locally still in evidence [32]. Vitamin A when injected in oily preparations is also less effectively utilized than when administered orally but if given to animals in propylene glycol its utilization is excellent [33, 34]. Steigmann and Popper [35] found that in man intramuscular administration of vitamin A did not appreciably raise the plasma vitamin-A level. Employing the intravenous, intraperitoneal or intrasplenic route Sexton *et al.* [36] observed no enhancement of the liver stores of vitamin A in the rat after the injection of aqueous colloidal solutions of carotene. Tomarelli *et al.* [37] demonstrated that when carotene is dissolved in Tween 80 (polyoxy-alkylene derivative of sorbitan monoleate) effective conversion of carotene to the vitamin occurred.

Under normal circumstances neither carotene nor vitamin A is excreted in the urine. In pneumonia and chronic nephritis vitamin A has been recovered from the urine and at autopsy the liver showed a lower reserve of the vitamin [38]. The influence of pneumonia is more pronounced than that of nephritis. Other febrile illnesses have also been noted to be associated with the urinary excretion of vitamin A Carotene is readily eliminated in the faeces but vitamin A to a much lesser extent. The faecal content of each is increased by the consumption of very large amounts of the respective substances and in gastro-intestinal dysfunction which impairs absorption. Both compounds undergo some destruction in the intestines and in the tissues.

Estimation and Sources of Provitamin and Vitamin A

Biological methods of assay measure the efficacy of the substance under examination in the prevention or cure of vitamin-A deficiency in animals [39]. The quantitative spectroscopic analysis is surveyed by Gridgeman [40] and the results are converted into international units by a conversion factor. Vitamin A shows an absorption band in the ultraviolet portion, the maximum being at 328 mμ. Of the chemical methods the most commonly employed is that of Carr and Price [41]. A 25 per cent solution of antimony trichloride in chloroform is used and a blue colour develops in the presence of vitamin A, maximal after ten seconds and thereafter rapidly fading; the blue colour is measured by a colorimeter or by spectrophotometric analysis. Carotenoids also give the Carr-Price reaction and it is necessary to examine the absorption spectrum of the colour to ascertain whether the absorption bands specific to vitamin A are present. Popper [42] noted that a greenish-yellow fluorescence was obtained by subjecting vitamin A to ultraviolet irradiation and so was able to ascertain the distribution of the vitamin in the tissues.

Synthesis of the carotenoids cannot take place in vertebrates and

the human sclera is of pale blue colour covered by a transparent layer of conjunctiva. Kruse [64] suggested that the earliest ocular changes of vitamin-A deficiency could be detected by biomicroscopic examination, a loss of transparency followed by thickening and then increase in vascularity of the conjunctiva constituting recognizable changes. Berliner [65] criticized the conclusions of Kruse and stated that the lesions were those ascribed to simple senile changes and the spots described were pinguecula. Jolliffe and Stern [66] found that in some subjects the lesions responded to massive vitamin-A therapy. Youmans *et al.* [67] did not consider that the histological changes of the conjunctiva were a satisfactory means of identifying vitamin-A deficiency in the adult. Limitations also appear to exist as to the value of the microscopic examination of sections of the skin and of vaginal scrapings.

Treatment of Vitamin-A-Deficiency States

The amount of vitamin A required in the therapy of deficiency states varies with the intensity and duration of the condition. As much as 600,000 I.U. daily may be necessary, although as a rule 50,000 to 100,000 I.U. suffice for the severe case and 15,000 I.U. daily for milder degrees of deficiency. Treatment should be persisted with over a long period since it may effect only a slow and gradual improvement. Large doses, in the region of 250,000 I.U., administered daily for several months, are indicated particularly for the dermatological manifestations.

The efficiency of the absorption of vitamin A and carotene diminishes as the size of the oral dose is increased; the vitamin should be administered in divided doses during the day [68]. Aqueous dispersions of vitamin A are more effectively utilised and absorbed than oily preparations. Vitamin A may be absorbed from the skin when applied in ointment form but there are marked differences in the absorptive rate and degree of different individuals, so that this method is unsatisfactory [69].

Carotinaemia and Hypervitaminosis A

While in animals large amounts of carotene ingested or injected produce no untoward effects, in man the consumption of large quantities of carotene-containing foodstuffs may lead to the condition of carotinaemia. A yellow colour develops in the skin—xanthosis cutis; in the milder examples the naso-labial folds and palms are particularly affected but in the more advanced the colour becomes generalized. The conjunctivae are spared, a point in the differentiation from jaundice. Carotinaemia is hardly a

satisfactory name since the blood normally contains a certain amount of the provitamin.

Babies fed on the breast milk of a carotinaemic mother may develop the condition [70]. Myxoedematous subjects on a normal diet may exhibit the syndrome and thyroid therapy induces its disappearance [71]. In the absence of the thyroid gland carotene is not metabolized to vitamin A [72]. Savy *et al.* [73] observed 5 cases of carotinaemia in patients suffering from hepatic disease. Diabetes, nephritis, cretinism and disorders of lipoid metabolism may predispose to an excess plasma content of carotene. In general, excessive consumption of carotene-containing foods and disorders which interfere with the utilization of the provitamin are conducive to carotinaemia.

A chemical method is available for distinguishing the condition. In a test tube equal quantities of serum, alcohol and petroleum ether are shaken up and then allowed to settle. The lipochromes dissolved in the petroleum ether appear as a distinct layer at the top and a yellow tinge denotes excessive carotene quantities. At the base of the tube lie the precipitated proteins and the middle zone contains the bile pigments [74] In itself carotinaemia does not appear to be a harmful condition and the accompanying symptoms are probably due to any associated disease or to the faulty nature of the diet.

Information on hypervitaminosis A in the human is scanty but Josephs [75] records the example of a boy aged 3 who was given a tablespoonful of halibut-liver oil (about 240,000 I.U. of vitamin A) daily from the age of 2 months. The child subsequently developed an abnormal liking for the oil and consumed large quantities. An increased serum vitamin-A and lipide content was associated with splenomegaly, hepatomegaly, hypoplastic anaemia, leucopenia and advanced skeletal development. Rapid improvement followed cessation of the intake of the oil. The toxic effects following the eating of bears' liver, the features of which are gastric upset, headache, irritability and exfoliation of the skin, are considered to be due to the high vitamin-A content of the organ [76]. Apart from a rare allergic reaction, there does not seem to be any danger in the administration of vitamin A in therapeutic dosages. The large reserves which can be built up in the body serve to prevent more than temporary rises in the plasma levels and only when this storage capacity is overwhe[illegible] massive dosage are toxic effects [

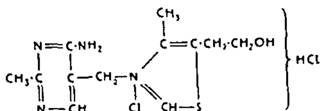
VITAMIN B_1

VITAMIN B_1 is also known as thiamine, aneurin, the anti-neuritic factor and the anti-beriberi factor. The term 'thiamine' was introduced because of the thiazole grouping in the chemical constitution of the vitamin. 'Aneurin' is an artificial abbreviation for an(ti-poly)neur(itisvitam)in. The use of 'anti-neuritic factor' in nomenclature is open to criticism, since, while neuritis may appear in disorders of nutrition, there are other types which do not originate from an avitaminosis; furthermore, deficiency of vitamin B_1 affects other parts of the nervous system, and may produce syndromes in which few, if any, signs of peripheral nerve involvement exist. Further research has revealed that beriberi is a multiple deficiency disorder, and that inadequacy of vitamin B_1 is but one factor concerned. The pioneer work of Eijkman [77] led to the appreciation of a close relationship between the ingestion of polished rice and the development of avian polyneuritis. The vitamin was synthesized by Williams and Cline in 1936 [78].

Chemical Properties

Vitamin B_1 is a white crystalline substance which is readily soluble in water and alcohol but not in fat solvents. It possesses a yeast-like odour. In the dry form it is very stable to heat, resisting a temperature of 100° C. for twenty-four hours, but it is thermolabile in alkaline and neutral solution. Strong acid solutions are not harmful and, in them, vitamin B_1 resists temperatures of 120° C., but with increasing alkalinity there is an increasing susceptibility to heat. Sulphite rapidly inactivates thiamine, thus affording the explanation of the loss of the vitamin following the sulphuring of fruits. The presence of acetates, borates and nitrites enhance the destructive properties of heat, and in themselves tend to disrupt the molecular arrangement of the vitamin. Thiamine is inactivated by oxidative and reduction processes and by ultraviolet light, in which it shows two bands, the absorption spectrum varying with the pH. Vitamin B_1 is a base and forms salts. It can be adsorbed on fuller's earth, charcoal and other substances. The graphic formula of thiamine hydrochloride ($C_{12}H_{18}ON_4SCl_2$) is as follows (page 23): –

Vitamin B_1 contains a pyrimidine and a thiazole ring, into which component parts it can be split up by hydrolytic cleavage. When thiamine is subjected to mild oxidation in an alkaline solution, such as alkaline potassium ferricyanide, thiochrome is



formed. Thiochrome is a yellow substance, giving an intense sky-blue fluorescence in ultraviolet light.

Units of Vitamin B_1

The vitamin-B_1 content of a substance should be expressed in milligrams of the crystalline compound. Prior to the synthesis of the pure product, it had been the custom to use the international unit, which represented 10 mg. of a standard preparation of an acid clay adsorbate One mg of the crystalline substance approximates to 330 I U It is no longer desirable to retain the international unit in reference to thiamine. The Smith curative unit, the Chase-Sherman unit, and the Roscoe unit are derived from biological methods of estimation and are now of little practical importance.

Metabolism of Vitamin B_1

Thiamine is absorbed from the small and large intestine, and in its passage across the wall of the intestine probably undergoes no change in composition. Absorption is rapid and fairly complete, but there appears to be an individual variation in this capacity. The presence of hydrochloric acid in the gastric juice is necessary for satisfactory absorption. From the blood stream, the liver and other tissues remove the vitamin and store it after phosphorylation, as cocarboxylase. A reversal of this procedure occurs as required, the cocarboxylase being dephosphorylated and the free vitamin passing into the blood. The body is able to store vitamin B_1 only temporarily and only in limited amount. Man cannot increase his stores of thiamine above this saturation by additional intake of the vitamin. Compared with vitamin A the content of vitamin B_1 normally found in the tissues is insignificant. A previous surfeit of the vitamin does not significantly lengthen the survival time of an animal placed on a thiamine-free diet. The concentrations of thiamine in human tissues are low, and are less than those of the corresponding tissues of several animal species. Deprivation of thiamine effects considerable diminution of the tissue concentrations, the brain conserving its supply to a greater degree than other organs. Ferrebee *et al.* [79] estimated that heart muscle was

richest in thiamine concentration, containing 2–3 micrograms
gram; brain, liver and kidney contain 1 microgram per gram,
skeletal muscle 0·5 microgram per gram. In the rat, Leong [
demonstrated that following saturation with vitamin B_1 the lar
amount stored in the body was contained in the muscles, altho
the actual concentration therein was but a fraction of that in
heart or liver. The muscles show the first and most compl
evidence of thiamine depletion in deficiency states. The to
amount of vitamin B_1 in the human body under ordinary circu
stances is about 25 mg.

Within the blood vitamin B_1 predominantly exists as cocarbo
lase. Cocarboxylase is an ester of thiamine, thiamine pyrophospha
it is also known as diphosphothiamine. The small amount
circulating free vitamin is found in the serum, cocarboxyl
forming the cellular constituent. While there is agreement that
level of free thiamine normally remains constant at 0·5 microgr
per 100 c.c., different figures have been advanced for the total co
centration of the two forms of vitamin B_1 in the blood, and th
have ranged from about 3 to 16 micrograms per 100 c.c. So
ten times as much of the vitamin is present in the leucocytes as
the erythrocytes [81].

The faeces contain thiamine which has not been absorbed a
that which has originated from bacterial synthesis. Both the fr
vitamin and cocarboxylase are recoverable from the urine, t
latter in very small quantity. Marked variation has been report
in the urinary excretion in different individuals on similar lev
of thiamine intake [82], and Mickelsen *et al.* [83] considered th
this was a characteristic of the individual, the explanation of whi
was not forthcoming from examination of the faecal excretion, t
degree of physical activity, the basal metabolic rate or the bod
weight. Administration of vitamin B_1 orally or parenterally
reflected in an increase in the urinary thiamine content, but th
represents only a fraction of the total amount administered. It h
been assumed that since the storage capacity of the body is so limite
much of the vitamin is inactivated in the tissues; even continue
supply of large doses of thiamine is accountable for in but sma
measure by the quantity excreted in the urine. A different interpre
tation has been offered by Alexander and his colleagues [84]. Th
urine contains substances other than thiamine which are capab
of accelerating yeast fermentation. The pyrimidine portion of th
thiamine molecule also possesses this property, and Alexander
al. hold that the urinary elimination of pyrimidine plus thiamin
accounts for practically all the vitamin B_1 which is administered.

Pyrithiamine is the name which has been applied to a pyridin
analogue which has been found to inhibit the growth of fungi [85]

This compound manifests a pronounced anti-thiamine action and, when administered to animals, can produce signs of a vitamin B_1-deficiency state, affording an example of interference with biological processes by analogues of the essential nutrient.

A substance can be extracted from fresh fish which is destructive to thiamine, and to which the name 'thiaminase' has been applied. Chastek's disease, a form of paralysis, is a dietary disease, first observed on the fox farm of J. S. Chastek of Glencoe, Minnesota. The disorder was produced by the inclusion of 10 per cent or more of uncooked fish in the ration of the fox, and was curable by the ingestion of adequate amounts of vitamin B_1. The post-mortem changes in the central nervous system closely simulated those of Wernicke's syndrome. Thiaminase is thermo-labile, and the active principle has been prepared in powder form. Deutsch and Hasler [86] found 15 out of 31 species of freshwater fish capable of producing Chastek's disease, but only 1 of 9 species of saltwater fish. However, some saltwater fish, including herring, whiting and mackerel, have anti-thiamine properties; clams show a similar activity, but no thiaminase is evident in oysters, caviare and smoked salmon [87]. The possibility of harmful consequences in man, following the consumption of raw or partially cooked fish products, arises and is supported by the demonstration of some 50 per cent destruction of the thiamine in the alimentary tract succeeding the ingestion of raw clams.

Estimation of Vitamin-B_1 Content

Various biological methods have been employed for the determination of the thiamine content of a substance. Pigeons, maintained on a diet of polished rice, develop paralytic symptoms and head retraction. Graded doses of the substance tested are administered, and their curative or preventive effects estimated. There are many drawbacks to this method. The rat-growth test is performed in a similar manner. The bradycardia method is based on the development of a sinus bradycardia in rats suffering from a vitamin-B_1-deficiency, and the response of the heart rate to the administration of the test material. Thiamine stimulates the growth of *Phycomyces blakesleeanus*, but the value of this action in thiamine determination is doubtful since other substances have a like effect. The production of carbon dioxide by yeast is enhanced by the presence of vitamin B_1, and this property is utilized in the yeast fermentation method. Conversion of cocarboxylase to vitamin B_1 is achieved by the addition of such substances as diastase or kidney extract.

Of the chemical procedures, the thiochrome and diazo tests are of value. In the thiochrome method the vitamin B_1 is adsorbed on

fuller's earth or similar substance, eluted and then converted to thiochrome by alkaline oxidation; thiochrome is estimated fluorometrically. Among the agents which may interfere with the thiochrome method are quinine, salicylates and nicotinic acid in large doses, if ingested shortly before the performance of the test. The diazo test measures the free vitamin and involves the measurement of a coloured azo dye following the subjection of the test material to a series of chemical reactions.

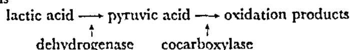
Sources of Vitamin B_1

Without the inclusion of whole grain cereals or enriched flour, the selection of a diet adequate in thiamine content is a difficult matter. In America the use of enriched flour is permissible, and the flour must contain at least 1·66 mg., and not more than 2·5 mg., of the vitamin per pound if the term 'enriched' be applied to the product; the other stipulations are a content of riboflavin between 1·2 mg. and 1·8 mg., of nicotinic acid or its amide between 6 mg. and 9 mg., and of iron between 6 mg. and 24 mg. per pound of flour. The use of high extraction flour in Britain in the preparation of bread has allowed of a satisfactory intake of thiamine. The bulk of the thiamine of grains is contained in the germ and outer layers; these tend to be removed in the milling process, and consequently most of the vitamin is lost. Although vitamin B_1 is widely distributed, it is present in most foodstuffs in only moderate amounts. Whole wheat, oatmeal and wholemeal cereals, dried yeast, pulses and pork are among the richest sources. Vegetables and fruits contain only small quantities, although the vitamin is found in fair concentration in seeds and legumes. Other good sources are nuts, eggs, and, to a lesser degree, meat, whereas milk offers a poor supply. Dried brewers' yeast is an excellent source of the vitamin, but live bakers' yeast actually interferes with the thiamine nutrition of the individual, and produces an increased excretion of vitamin B_1 in the faeces and a reduction of urinary thiamine to subnormal levels [88]. Under the latter circumstances decreased absorption of the vitamin occurs, and this is considered to be attributable to the inclusion of the thiamine in the metabolism of the live yeast cell [89]. Fish are poor in thiamine content.

Action of Vitamin B_1

Thiamine is concerned in carbohydrate metabolism. As cocarboxylase, it acts as a co-enzyme. Lactic acid is converted to pyruvic acid, the loss of hydrogen occurring through the agency of a dehydrogenase. Further degradation of pyruvic acid by oxidation

requires the influence of cocarboxylase. Diagrammatically the process is



Carbohydrate oxidation does not always involve the formation of pyruvic acid, and this substance may appear in the katabolism of protein and possibly of fatty acids [28]. Pyruvic acid ($CH_3.CO.COOH$) is acetylformic acid, and its concentration in the blood, cerebrospinal fluid and urine increases in vitamin-B_1-deficiency states in man and in animals. Excess of pyruvic acid inhibits the breakdown of lactic acid by the dehydrogenase, so that lactic acid also accumulates in the tissues. Carbohydrate metabolism is a complex and difficult subject, but the above oversimplified version of the mode of participation of thiamine suffices for present purposes, and for the appreciation of the importance of vitamin B_1 in the nutrition of the nervous system which is dependent on normal carbohydrate metabolism for its capacity to function normally.

Another action of thiamine has been suggested in connexion with the transformation of fat to carbohydrate. The vitamin was considered to be necessary for this reaction.

Human Requirement of Vitamin B_1

Much confusion has arisen in the estimation of human requirements of thiamine on account of the different criteria which have been adopted. Experimental human subjects may subsist on a thiamine-restricted diet for considerable lengths of time and experience no subjective ill-effects. Changes which are detectable by other than clinical methods have also proved unreliable in the assessment of thiamine needs The urinary excretion of the vitamin has been measured as an indication of man's minimal allowances. Holt [90] based the estimation of human requirements on the ability to protect against beriberi, the excretion of a definite portion of a test dose of the vitamin, the control of the blood pyruvate concentration, and the prevention of the early manifestations of a deficiency state; he arrived at a figure of 0·13 mg. to 0·17 mg. per 1,000 calories. Alexander and Landwehr [91] concluded that 0·44 mg. of thiamine per 1,000 calories provided the minimal allowances for a normal male whose caloric intake was 2,400 per day. The Food and Nutrition Board of the National Research Council of the United States (1948) recommend a minimal dietary allowance of thiamine of 1·2 mg. to 1·8 mg. per day for man (154 lb. in weight) according to the level of his activity, and for

woman (123 lb. in weight) 1·1 mg. to 1·5 mg. under circumstances. Melnick [92] assesses the value at 0·35 1,000 calories. Holman [93] concluded that there is a w crepancy between the estimates of the amounts require problem is further complicated by the lack of definite kn of the degree of participation of biosynthesis of vitami human nutrition. It would appear that under ordinary co the American recommendations offer a satisfactory margin o

Certain physiological factors influence man's requir The food intake is important and especially the quan carbohydrate ingested. Cocarboxylase is spared in fat meta this is demonstrated in animals fed a diet rich in fat and thiamine, when good growth may continue and polyneur ensue. The human diet rarely undergoes sufficient change content to render this action of fat of much clinical signi The protein content of the diet is also considered to red utilization of thiamine. Uniformity of diet necessitates a thiamine requirement than does a varied one. Exercise *per* no significance, and the increased demands of thiamine aris the increase in total caloric value of the food intake. C conditions and excessive perspiration affect the thiamine allo in no appreciable degree. Pregnancy and lactation present problems. Increased basal metabolic rates, as in hyperthyr and febrile illness, prolonged diuresis, whereby the vita excreted in excess in the urine, and diarrhoeal conditions d increased allowances. Digestive disorders may lead to defici intake and of absorption, and achlorhydria exerts a dele effect. Rapid emptying of the stomach into the duodenum e the vitamin to the destructive action of the alkaline contents duodenum; the external secretion of the pancreas, the bile and an prescribed medicinally tend to inactivate thiamine. This susce ity to alkaline reactions probably explains the larger quantity vitamin excreted in the urine when administered after a mea before food consumption. Among the vitamin-B_1 deficiency sta those arising from the institution of therapeutic measures. Rest dietary intakes and the prescribing of thyroid and dinitropheno be mentioned in this respect. The intravenous infusion of soluti glucose is a common procedure in surgery; unless adequate int thiamine is maintained, a deficiency state may arise if large qua of glucose are administered, especially in patients whose dietar sumption prior to operation had been low.

Vitamin-B_1 Deficiency in Animals

The influence of vitamin B_1 on growth is probably a secon

non-specific effect. Acute thiamine deficiency in the pigeon produces opisthotonos, lateral rotation of the head and loss of thermal control, these manifestations rapidly responding to thiamine administration. Chronic deficiency in pigeons leads to the development of spastic paresis of the wings and legs, severe prostration and cardiac lesions; widespread changes are found in the nervous system, appearing first in the peripheral nerves and spreading to the brain and spinal cord, in proportion to the severity of the deficiency. The bradycardia of vitamin-B_1-deficient rats has already been referred to, and at a subsequent stage weakness and paralysis of the limbs appear. It is not possible by dietetic restrictions to induce a thiamine deficiency in cattle and other ruminants, because of their ability to exist on endogenous supplies of the vitamin. Neurological features predominate in the dog and cat. Much of the pathological work in experimental animals is obscured by the difficulty in segregating the lesions attributable to simple inanition, which in itself is capable of yielding structural changes in the nervous system. Anorexia in vitamin-B_1 deficiency may be so marked that emaciation ensues. In animal experiments it is essential to restrict the diet of the controls to the amount voluntarily consumed by the thiamine-deficient animals. Acute deficiency states may be attended with but little morphological alterations, the clinical features depending on biochemical changes.

Vitamin-B_1 Deficiency in the Experimental Human Subject

Many symptoms referable to thiamine deficiency develop long before the appearance of beriberi. These earlier manifestations are difficult to distinguish from the neurasthenic syndrome, and include loss of appetite, undue fatigability, insomnia, headache, vague body pains and gastro-intestinal disturbances. Wilder [94] investigated the effects of a moderate restriction of vitamin B_1 on a group of female inmates of a psychiatric hospital; in almost every case cessation of the experiment became necessary by reason of the anorexia induced. Changes of behaviour, progressively decreasing ability to perform accustomed tasks, irritability, headache, hypersensitivity to painful stimuli and noise, paraesthesias and loss of manual dexterity were some of the clinical features which developed; the blood pressure was low in all cases, and vasomotor lability marked. Wilder expressed the opinion that the psychological component of pellagra and other multi-vitamin-deficiency states may be largely attributable to deficiency of vitamin B_1. Williams *et al.* [95] administered a diet containing not more than 0·1 mg. of thiamine per 1,000 calories, but adequate in all other respects, to human volunteers. Anorexia, lassitude and

lack of energy ensued. Paraesthesias were complained of, and at a later stage objective evidence of neurological lesions appeared in the form of defects in the cutaneous sensory pathways, diminution or disappearance of the tendon reflexes and paralysis of the muscles of the thighs and legs. Response to the administration of large doses of thiamine was obtained, but only after many weeks of therapy. They concluded that the outstanding features of a pure vitamin-B_1 deficiency in man would appear to be anorexia, fatigue and symptoms of a polyneuropathy. Keys and his colleagues [96, 97] conducted studies on the effects of border-line deficiency states of vitamin B and of acute vitamin-B deprivation. On a daily intake of 3,300 calories, the thiamine allowances were 0·18 mg., the riboflavin 0·25 mg. and the nicotinamide allowances 3·5 mg., each per 1,000 calories. The duration of the experiment was 161 days and no significant changes were noted in physical fitness, psychomotor activity, cardiac function, sensory function, intellect and personality evaluations. Two of their subjects, having existed on the above dietary arrangements, were immediately afterwards placed on a diet containing negligible amounts of the three vitamins for a period of twenty-three days. Progressive anorexia and progressive deterioration in endurance and co-ordination developed, but there was little, if any, adverse influence on strength, vision, hearing or speed. This investigation revealed that thiamine was the limiting factor, since vitamin-B_1 administration alone relieved the symptoms. While a restricted intake may for some time produce no apparent clinical untoward effects, a sudden more pronounced decrease of thiamine intake may precipitate overt manifestations of a vitamin-B_1-deficiency state. The body stores of thiamine are effective in protecting against severe deprivation for, at most, a few weeks. The findings of these and other investigations of a similar type indicate that, although deficiency of thiamine results in functional defects of the peripheral nerves, since frank beriberi was not produced, it is probable that beriberi is not attributable to lack of thiamine alone. No mention in this section has been made of the cardiac changes under the experimental conditions, nor of the biochemical abnormalities; these aspects are dealt with elsewhere.

Detection of Thiamine Deficiency by Laboratory Methods

A. *Blood Thiamine Level.* – The determination of the total blood content of vitamin B_1 has proved of no value as an index of thiamine nutrition. Normal values show so wide a range as to afford little evidence of early deficiency states. The blood thiamine of the individual is relatively static and does not decrease significantly

until severe clinical expressions of the deficiency are present [98, 99].

B. *Urinary Excretion of Vitamin B_1.* – Melnick [100] found a good correlation between the urinary excretion of vitamin B_1 and the adequacy of the dietary level. Normally, individuals with satisfactory intakes of thiamine excrete that excess of the vitamin which is beyond their requirements, or which is not required for tissue storage. The subject deficient in thiamine attempts to conserve his supplies by reducing the urinary excretion of the vitamin. This conclusion has been upheld by the findings in experimental deficiency studies conducted on the human subject. The disadvantages of employing the estimation of the urinary content lie in the marked difference of opinion that exists as to the normal excretion values, and in the fact that a reduction of thiamine intake is attended by a rapid diminution in the urinary excretion, even while the tissue reserves remain high. A more satisfactory method has evolved and utilizes the administration of a 'test dose' of thiamine, and the measurement of the quantity which subsequently appears in the urine. In thiamine deficiency the depleted tissues replenish their stores and little is lost in the urine. Successive daily doses of the vitamin may be administered, and the degree of deficiency gauged on the number of days necessary to elevate the urinary concentration of thiamine to normal values. More frequently a single test dose is used, and this may be supplied by the oral or parenteral route. If too large a quantity of thiamine be supplied in the one dose method, its excretion in the urine may be so high that the deficiency state escapes detection. Absorption defects due to gastro-intestinal dysfunction may occasion misleading results. The vitamin is excreted in the urine in greater quantity when ingested after a meal than when the stomach is empty Melnick and Field [101] observed a prompt response of the urinary thiamine concentration to variations in thiamine intake in normal subjects whose diet was found to contain about 1 mg. vitamin B_1 per day. From this study they concluded that an intake of this amount per day suffices to furnish a saturated state of the tissues. Robinson *et al.* [102] suggested the following method of performance of the test: After breakfast 5 mg. of vitamin B_1 are ingested; the excretion of less than 8 per cent of the dose in the twenty-four-hour urine is judged as definite evidence of deficiency. A number of modifications in the procedure have been introduced by other investigators, with corresponding different standards of assessment of deficiency. Parenteral administration obviates the possibility of absorptive differences interfering with the results. The intramuscular or intravenous route is employed, and here again there exist different modifications of the technique of the test. Mason and Williams [103] inject 1 mg. of thiamine intramuscularly and

X-ray examination of the heart, the changes in the electrocardiogram, and the measurement of the circulation time are discussed later. Lowered glucose tolerance curves may be found in conditions of thiamine depletion, but are not of sufficiently marked degree to prove of value in diagnosis.

Treatment of Vitamin-B_1 Deficiency

In the British Pharmacopoeia there are aneurinae hydrochloridum (thiamine chloride) and pulvis vitamin B_1, which is an adsorbate on fuller's earth. The United States Pharmacopoeia contains thiamine hydrochloride and tabellae thiaminae hydrochloridi. As in all nutritional deficiency syndromes, a satisfactory diet must be prescribed, and recognition given to the polyvitamin insufficiency present. Large doses of thiamine alone in a deficiency state may precipitate signs of a deficiency state, not formerly evident, of another vitamin. Acute deprivation rapidly yields to treatment, but chronic cases require long and persistent therapy and perhaps only some of the clinical signs will respond. The degree of irreversibility can only be judged on the therapeutic results. It is pointed out by Alexander and his co-workers [112] that the major portion of thiamine administered in daily doses of more than 10 mg. is rapidly excreted in the urine, and they did not consider that there was any justification for the use of larger doses than 34 mg. daily by the parenteral route. The latter method will be required in acute manifestations of the disorder, and when for some reason the oral route is contra-indicated. Brewers' yeast, rice polishings, and wheat germ are excellent sources of the B vitamins, and liver preparations are valuable. Further measures are detailed under the section on beriberi.

CHAPTER FOUR

THE VITAMIN-B COMPLEX – NICOTINIC ACID – RIBOFLAVIN – BIOTIN – CHOLINE – PANTOTHENIC ACID – INOSITOL – PYRIDOXINE – PARA-AMINO-BENZOIC ACID – FOLIC ACID

IT WAS not until 1926 that it was recognized that 'vitamin B' consisted of more than one factor [113, 114]. A subdivision into two portions only was appreciated at that time, one a thermolabile anti-neuritic vitamin, and the other a thermostable anti-pellagra vitamin. To the former the term vitamin B_1 was applied, and to the latter vitamin B_2. Several properties were ascribed to vitamin B_2. Pellagra in man could be prevented by its administration, as could black-tongue in dogs and the pellagra-like dermatitis in rats; it was essential for the growth of rats. The anti-neuritic factor was also referred to as vitamin F and the A.N. (anti-neuritic) factor. Further designations of vitamin B_2 were the P P. (pellagra-preventing) factor and vitamin G. These terms are now but rarely used and vitamin F is employed in another connexion. Further investigation resulted in the realization that vitamin B_2 was not a single vitamin but a complex made up of several components. Each of these components will be described under separate headings. It is probable that even this large list of substances does not represent all the members of the vitamin-B_2 complex.

Vitamins B_3, B_4, B_5 and B_7 had been assumed to represent separate and distinct components of the vitamin-B complex but there is little justification for such a view. Similarly vitamin B_8 or adenylic acid has not been established as a specific vitamin.

NICOTINIC ACID

The term 'nicotinic acid' was introduced following the first laboratory preparation of the substance by the oxidation of nicotine. The relationship of these two compounds otherwise is remote. The amide of nicotinic acid, nicotinamide, is a member of a complex enzyme system. Since it was considered that the use of 'nicotinic acid' and 'nicotinic acid amide' in nomenclature might occasion unwarranted apprehension in the minds of the public, the respective substitution of 'niacin' and 'niacinamide' was suggested, with the recommendation that the former names be the first choice in scientific literature [115]. Another synonym which has been employed for nicotinic acid is the 'Pellagra-Preventive factor' or the 'P.P. factor'. Pellagra is now recognized to be a

concerned with the reversible oxidation-reduction changes of the co-enzyme factor. In nicotinic-acid-deficiency states the co-enzyme content of the tissues is diminished.

Units, Estimation and Sources of Nicotinic Acid. – The isolation of nicotinic acid in the pure state occurred before its vitamin qualities were appreciated. Accordingly no units other than the weight of the compound were required to express the nicotinic-acid content of a substance.

Pyridines react with cyanogen bromide and a measurement of the colour change affords a means of their estimation. The test is not specific for nicotinic acid since other pyridine derivatives are simultaneously estimated. A similar objection applies to the 2 : 4 dinitro-chlorobenzene chemical method. Growth of *Lactobacillus arabinosis* and other organisms has also been employed in the determination of nicotinic acid and nicotinamide quantity and offers a more satisfactory procedure. Various biological methods have been applied and measure the preventive or curative action of the substance under examination against the features of a deficiency.

Nicotinic acid is a necessary component of all living cells. Man obtains his requirements from his food and probably also from biosynthesis in the alimentary tract. Not all animals require nicotinic acid or its amide in the pre-formed state and typical signs of deficiency are found only in the dog, pig and monkey in experimental studies. Excellent sources are liver, yeast, kidney, adrenals, meat, brain, peanuts and whole grain products. Fruits, vegetables and milk are poor in nicotinic-acid content and only small amounts are present in fish, egg yolk and white bread. Milling of the grain removes most of the vitamin so that polished rice and white flour are inadequate as dietary suppliers of nicotinic acid. The vitamin exists as the amide or as a component of co-enzymes within the living cell; little, if any, free nicotinic acid is present.

Adult Human Requirements of Nicotinic Acid

Estimations of the minimum daily allowances for man were at first based on the quantity which was necessary to prevent the development of black tongue in dogs, on the assumption that the requirements of nicotinic acid per unit of weight for man and dog were about equal. Calculating from this surmise, for the particular age it was found that the nicotinic-acid requirements were roughly ten times those of thiamine. While there still remains some doubt about the exact minimal standards, the Food and Nutrition Board of the National Research Council of the United States (1948)

recommend a tenfold allowance over that of vitamin B_1. For man (154 lb. in weight) 12, 15, and 18 mg. and for woman (123 lb. in weight) 10, 12 and 15 mg. of nicotinic acid daily are recommended according to the degree of physical activity. Adults receiving diets of 2,00 ocalories or less require only 1 mg. of thiamine per day and hence only 10 mg. of nicotinic acid. As with other essential nutrients, whose biosynthesis has been demonstrated within the body, knowledge of the quantity available to man from this endogenous source is not yet determined and so cannot as yet be considered in the computation of man's allowances.

Nicotinic - Acid - Deficiency States. – Experimental nicotinic - acid deficiency in the dog is among the best known of the animal nutritional deficiency states. The symptoms are similar to pellagra. There is a severe stomatitis, diarrhoea, dermatitis and a slight secondary anaemia. The gross and microscopic examination of the pathological lesions shows a marked correspondence between the black tongue of dogs and human pellagra.

In man nicotinic-acid deficiency is found in association with pellagrous skin lesions, changes in the oral mucous membrane, gastro-intestinal derangement and with neurological and mental phenomena. These are discussed under pellagra and in the appropriate sections.

Detection of Nicotinic-Acid Deficiency by Laboratory Methods

(1) *Nicotinic-Acid Content of the Blood.* – This has proved a disappointing procedure in the detection of nicotinic-acid deficiency. No significant changes were recorded in pellagra [121]. In a group of 60 normal individuals Carter and O'Brien [124] found an average blood-nicotinic-acid level of 0 438 mg. per 100 c.c. with a range of 0·26 to 0·573 mg. per 100 c c. The blood concentration was temporarily increased after the administration of large doses of nicotinamide but showed no great change in a variety of pathological conditions. The above authors noted that hyperthyroidism, pernicious anaemia and sprue may be associated with low blood values, whereas myeloid leukaemia with a high leucocyte count is accompanied by high nicotinic-acid values. These investigators concluded that the concentration of nicotinic acid in the blood does not provide a useful nutritional index. In the measurement of the nicotinic-acid content of blood the whole blood is used since that quantity of the vitamin present in the plasma is negligible; nicotinic acid itself, as has been mentioned, exists in the blood in the free form in very small quantity and the estimation also includes the co-enzymes and nicotinamide.

(2) *Studies of Urinary Excretory Products.* – The daily quantities of

It crystallizes as fine orange-yellow needles, and is insoluble in fat solvents, sparingly soluble in water, and very soluble in alkali solutions. Aqueous solutions of riboflavin present a greenish-yellow colour, and show a striking yellow-green fluorescence. Visible and ultraviolet light exerts a profoundly deleterious action on the vitamin, which must be protected from such influences by rendering impervious to light the containers, in which the preparation is packed; the products resulting depend on the reaction of the solution, lumiflavin being formed in alkaline solution and lumichrome in neutral solution. Riboflavin is stable at ordinary temperatures and shows marked heat stability, especially in acid solution. Alkaline mediums rapidly inactivate the vitamin.

Unit, Sources and Assay of Riboflavin. – Riboflavin content is expressed in milligrams. The rat unit (Bourquin-Sherman unit) is the daily quantity which will maintain normal growth in a standard rat; it is an unsatisfactory measure of the vitamin, as many other factors essential for growth influence the results.

In its natural distribution riboflavin occurs as such, as riboflavin-5-phosphoric acid and as riboflavin-adenine-dinucleotide. The vitamin is present in all members of the plant and animal kingdom, being an essential constituent of every living cell. Among the best sources are brewers' yeast, liver, kidney, egg-yolk, milk and cheese; summer milk contains a greater proportion than does the winter product. Plant seeds have a small content, which rapidly increases during germination. The leaves of green vegetables show a high concentration, but there is a rapid fall as the leaves age and dry. In general, foods which provide a good supply of thiamine are rich in riboflavin. Riboflavin exists predominantly in the bound form in the plant kingdom. Plants, most bacteria, fungi and moulds possess the capacity to synthesize the vitamin.

Assay of riboflavin may be carried out in several ways. The growth response of the rat, chick, or *Lactobacillus casei* has been utilized. The characteristic absorption spectrum can be employed for the pure substance, the destructive effect of light being taken into consideration. The fluorescent spectrum and a measure of the lumiflavin, to which riboflavin is converted in alkaline solution, have also been employed.

The Physiological Action of Riboflavin. – The action of riboflavin in the body is described by Stannus [133]. Riboflavin is a component of chemical combinations, referred to as co-enzymes. These, in combination with specific proteins, the apo-enzymes, take part in the tissue metabolism of carbohydrate. Riboflavin, combined with

protein as a flavoprotein, alternately accepts and liberates two atoms of hydrogen, thereby oxidizing products of carbohydrate metabolism. Riboflavin is involved in several of the reactions concerned with the oxidation of carbohydrate in the tissues, since the co-enzymes are able to attach themselves to different apo-enzymes, each system conducting a specific reaction. In order that riboflavin be able to participate in these enzyme reactions, it must undergo phosphorylation, a process occurring in the intestinal mucosa and probably in the liver and other tissues. Stannus stresses the adverse action of ariboflavinosis on the integrity of the capillary endothelium, and thereby offers explanation of the various clinical manifestations of the disorder.

Metabolism of Riboflavin. – Absorption of the chemically bound riboflavin can take place only when the vitamin is liberated. Phosphorylation is necessary for absorption, and the capacity to form the phosphoric acid ester appears to reside in many tissues, allowing of absorption following parenteral injection of riboflavin. The hydrochloric acid of the gastric juice has a functional rôle in the absorptive mechanism. Intestinal disease may affect the phosphorylating activity, and thus lead to defective absorption. The liver, kidney and heart contain relatively large quantities of riboflavin, but no special storage sites are present, and high consumption of riboflavin does not effect any marked increase in the hepatic concentration; examination of the organs of animals which have succumbed to riboflavin deficiency shows them to contain approximately one-third of their normal riboflavin content [134], and no significant decrease in the riboflavin level of the blood is noted under these circumstances [135].

The urine is the main channel of excretion of the vitamin, smaller amounts appearing in the faeces The principal excretory product is free riboflavin, but as much as 50 per cent may be constituted by the phosphoric-acid esters Uroflavin can also be recovered from the urine, and is a pigment with a chemical structure and a function approximating to those of the vitamin. The biosynthesis of riboflavin in the intestines will explain the continued faecal elimination of the compound in states of nutritional deficiency, whereas the urinary content may sink to zero levels. Intravenous injection of riboflavin in animals which have been subjected to bilateral nephrectomy results in rapid excretion of the vitamin into the small intestine, especially the duodenum; excretion through the bile would appear to be an important factor in the elimination of riboflavin [136], but destruction of riboflavin proceeds at a rapid rate in isolated loops of the large intestine; in the small intestine absorption progresses at a faster pace than

destruction, and it is uncertain whether inactivation occurs at all in the small intestine under normal conditions.

Detection of Riboflavin Deficiency

The clinical manifestations of deficiency of riboflavin in man are general ill-health, characteristic changes in the oral structures, dermatological lesions and corneal vascularization. The oral and ocular features are detailed elsewhere. Sebrell and Butler [137, 138] described a dermatitis involving the alae nasi, naso-labial folds, eyelids, forehead and ears. A fine, scaly, somewhat greasy dermatitis appears on a lightly erythematous base. In more advanced stages filiform excrescences become evident [139]. Spies *et al.* [140] reported roughening of the skin around the mouth and across the tip of the nose due to the plugging of the hair follicles with sebaceous material, and to which they applied the designation of 'shark skin'. Encrustation may be present. Other parts of the body may demonstrate the skin lesions, and particular mention may be made of the vulvae, scrotum, penis, and perineal region. In general the distribution of the seborrhoeic changes are in relation to the various folds of the body. The lingual changes of ariboflavinosis may affect other mucous surfaces, and a vaginitis with leucorrhoea occur.

None of the above signs individually would appear to be diagnostic of a riboflavin-deficiency state, and other causes exist for each of them. It becomes evident that diagnosis from the clinical features alone must depend on the presence of a combination of the characteristic features, rather than on one individual manifestation. The therapeutic response may afford a satisfactory criterion.

It is unfortunate that laboratory procedures have not proved of great value. The blood content of riboflavin of 20 normal subjects was found to range between 0·35 and 0·45 microgram per c.c., and a similar range was discovered in a group of patients suffering from varying degrees of riboflavin deficiency; the muscle riboflavin concentration of 9 control subjects ranged between 2·2 and 3·5 micrograms per gram of fresh weight, and no deviation from this range was noted in 30 pellagrins. Accordingly, Axelrod and his colleagues [141] concluded that an evaluation of the blood or muscle riboflavin values was not satisfactory in the elucidation of ariboflavinosis. A saturation test was suggested; 16 micrograms of riboflavin per kilogram of body-weight were injected intravenously, and normally more than 25 per cent should be excreted in the urine in the following four hours. The value of this and similar procedures is debatable. Estimation of the urinary products of elimination is of little significance, since this merely reflects the immediate

intake [142]. Studies conducted on adult male prisoners showed that after the ingestion of riboflavin supplements an increase of riboflavin appeared in the urine; the retention of such supplements varied from 17 to 80 per ce [illegible] fluctuations [143]. It wo [illegible] tests with the test dose of [illegible] misleading results.

Minimal Human Requirements of Adults

The recommended daily allowances of the Food and Nutrition Board of the National Research Council of the United States of America (1948) for a man of 154 lb. weight are 1·8 mg., and for a woman of 123 lb weight 1·5 mg. These recommendations were based on the relationship of the riboflavin requirement of growing animals to the thiamine requirement, which was found to be in the approximate proportion of three to two. Since knowledge of the thiamine needs is more exact than that of the riboflavin, the riboflavin allowances were estimated in accordance with this ratio. These suggested quantities would appear to offer a wide margin of safety. Williams *et al.* [144] stated that an intake of 0·5 mg. per 1,000 calories is sufficient for maintaining satisfactory tissue levels. Keys *et al.* [145] observed that normal young men suffered no physiological handicap from subsistence for at least five months on a diet providing 0·31 mg. of riboflavin per 1,000 calories. Hagedorn *et al.* [143] detected no physical findings indicative of riboflavin deficiency in men who for two years or more had been ingesting a daily content of riboflavin of not much more than 0·5 mg.

Treatment of Riboflavin-Deficiency States

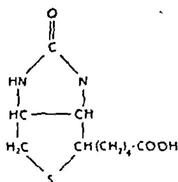
The oral route of administration is preferable, the vitamin being readily absorbed from the alimentary tract. Intravenous or intramuscular injection has been employed without the occurrence of undesirable reactions, and is indicated when for some reason the patient is unable to take the vitamin by mouth, or when a gastro-intestinal derangement interferes in marked measure with absorption. An intramuscular injection may be given at the onset of treatment in order rapidly to increase the tissue content of the vitamin, but the urinary excretion following intravenous administration is large and rapid and renders this route relatively unsatisfactory Since riboflavin deficiency is practically always present in association with deficiencies of other vitamins, the intake of riboflavin alone is undesirable, and may occasion severe symptoms

referable to an inadequacy of another essential nutrient, the manifestations of which had hitherto not been apparent. The average oral dose sufficient for curative purposes is 3 or 5 mg. thrice daily. Larger doses, up to 50 mg. a day, are prescribed in severe degrees of ariboflavinosis, but with amounts beyond this an increasing proportion is lost through urinary excretion. Toxic reactions do not appear to follow riboflavin therapy. The response to adequate treatment is promptly exhibited, the symptoms disappearing within a few days, although the objective features persist for some weeks or longer.

BIOTIN

Biotin is also known as vitamin H and co-enzyme R. 'Bios' was the term originally applied to substances stimulating the growth of yeast. Vitamin H was derived from the German word, Haut (skin). Co-enzyme R refers to the essential rôle of the vitamin in the growth of Rhizobium, a nitrogen-fixing organism. Biotin was isolated in 1936 [146] and was synthesized in 1943 [147].

Properties. – Biotin is a crystalline substance which is soluble in water and alcohol. It shows poor solubility in fat solvents. The formula is $C_{10}H_{16}O_3N_2S$ and the chemical structure is



Acids and alkalis do not exert a destructive effect and the vitamin is heat stable. Oxidizing agents inactivate biotin. It is a constituent of every type of living cell and has a wide natural distribution although present in only very low concentrations. Biotin occurs both in the free and bound form; the former is present predominantly in fruits and grasses and the latter in yeast and animal tissues, while vegetables, grains and nuts contain both [148]. Biotin found in egg yolk (α-biotin) is claimed to differ from that present in liver (β-biotin). The richest sources are liver, yeast, kidney, pancreas, adrenals and cereals. The bound insoluble

form, as it occurs for example in the liver, can be freed by autolysis or by hydrolysis with acids or enzymes such as trypsin [149].

Assay. – No chemical method is as yet available for the estimation of biotin and biological procedures are employed. These measure the growth of yeast or bacteria, or the quantity of acid produced by certain organisms. The rat test depends on the protection afforded against egg-white injury. The chick is used in similar manner and is preferable to the rat. A 'rat unit' signifies that amount of biotin which when given daily will cure egg-white injury produced in the rat by a special diet. The 'saccharomycetes unit' refers to the quantity of biotin capable of producing a 100 per cent increase in the growth of a specific strain of yeast under controlled conditions.

Function and Metabolism. – Biotin is essential for the normal growth of almost every animal, and for the growth of numerous strains of yeasts, bacteria and fungi; those micro-organisms which do not require the addition of biotin to the medium would appear to possess a capacity to synthesize the vitamin. The intimate connexion with growth is emphasized by the relatively high concentration found in embryonic and neoplastic tissue. Synthesis of the vitamin occurs in the intestine of man.

Little is known of the physiological function of biotin in man. The vitamin would appear to possess no marked pharmacological activity since no changes in the blood pressure, heart rate or respirations were observed following its administration to anaesthetized rats, and the excised uterus and intestine of rabbits were unaffected when suspended in concentrations of the vitamin [150]. Normal human subjects on unrestricted dietary intakes excreted in the urine from 14 to 111 micrograms per twenty-four hours, and the daily faecal content varied between 86 and 191 micrograms; the combined quantities were three to six times as great as that present in the diet [151] A striking increase in the urinary excretion followed the oral administration of a large dose of crude biotin, but it was noted that, on a constant daily biotin intake, a constant urinary content for the individual occurred, although this figure varied widely in different individuals Oppel also determined that the urinary biotin consisted of an avidin-combining and a non-avidin-combining fraction, and he found the quantities in the urine to be within normal range in a wide variety of diseased states. The avidin-combining portion varies with the amount of biotin ingested, while the other urinary constituent remains constant under these conditions.

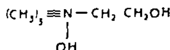
Biotin is readily absorbed from the intestinal tract. Storage of the vitamin to some extent is evident in the liver and kidneys. The requirements of the human organism have not been determined, the question of availability of the vitamin from intestinal

and the feeding of egg white might prove of value in retarding the progress of the tumour. The results obtained, however, have not been encouraging.

CHOLINE

Considerable doubt has been cast on the validity of a vitamin status for choline. McHenry and Patterson [165] are of the opinion that choline does not act as a vitamin in the body and that it would be best to leave choline unclassified, although there is no question of the substance being an essential constituent of the diet when supplies of methionine and ethanolamine are markedly restricted. It is, however, convenient at present to include a discussion of choline in a treatise on vitamins.

Properties. – The term 'choline' first appeared in the literature in 1862 [166]. Choline is a colourless, viscid fluid and choline chloride is a white crystalline substance, of a salty bitter taste and of marked hygroscopic activity. The distribution in nature of choline is very wide both in the animal and plant kingdoms. Since it is a constituent of lecithin, good sources are meats, cereals, vegetables and eggs; yeasts may contain large amounts but show variability in this respect. The content of dietary substances has been presented by Fletcher *et al.* [167] and by Engel [168]. Animal organs, egg yolk and nervous tissue contain considerably more choline than does plant material [169]. Choline has the following chemical structure: –



Choline is a strong base and is soluble in water, alcohol and formaldehyde. The major portion of choline in the blood is present in the plasma, only a small amount existing in the cells. The free choline content of human plasma was estimated at between 44 and 75 micrograms per c.c. [170]. It was also found that the choline in the urine existed entirely in the free state, the daily excretion of four normal adults varying between 5·6 and 9·0 mg.

Among the compounds which are capable of supplying transferable methyl groups are choline, betaine (the anhydride of choline) and methionine. The body does not possess an ability to produce the methyl groups for transmethylation and must rely on methyl donators. Choline is thus essential for normal nutrition since it supplies methyl groups for the formation of phospholipides in the tissues whose function is concerned with fat transport. Not all compounds containing a methyl group in their structure are

available for transmethylation. Betaine is only one-third as effective as choline in its lipotropic influence, suggesting that only one methyl group is available for transmethylation [171]. Choline synthesis is constantly taking place in the body and, when the dietary choline is insufficient, biological methylation of suitable nitrogenous substances produces a supply of choline which will tend to maintain choline concentration at a constant level. Choline is a lipotropic substance and, in its absence, fatty changes develop in the liver.

Deficiency States in Animals. – Lack of choline is accompanied by hepatic changes which are discussed elsewhere. Degenerative lesions in the kidneys were also observed in young rats which at weaning were fed a diet containing inadequate supplies of choline; older animals did not manifest the renal disorder [172]. Marked haemorrhagic degeneration of the kidneys, splenomegaly and a regression of the thymus constituted the features of the syndrome in addition to the fatty liver. The administration of cysteine to the diet increased the severity of the kidney damage [173] Histological examination of the kidneys revealed a tubular degenerative process, hyperaemia and haemorrhages and, in advanced cases, actual calcification of the tubules. The causative mechanism of the renal pathology has been under dispute but McHenry and Patterson [165] consider that since all the substances which prevent the condition are lipotropic agents, the failure of synthesis of phospholipide formation in the liver with resulting deficiency of phospholipide in the kidney, explains its origin. Renal derangement can be produced at any time during the period of rapid growth [174] during which time a supply of phospholipide would appear to be particularly essential for the development of new cell structure.

In rats deficiency of riboflavin [175], thiamine [176], pyridoxine, choline or protein [177] may produce ulceration and hyperplasia of the fore-stomach. The action of the protective vitamin factors is interdependent, so that a deficiency of one interferes with the effective prophylactic function of the others; choline represents only one of several essentials for protection against the gastric abnormalities.

Perosis ('slipped tendon') in turkeys and chicks is characterized by hock enlargement, distorted metatarsi and slipped tendons. It would appear that deficiency of several different dietary constituents is capable of its production; manganese, biotin and choline especially in conjunction with the vitamin-B complex, are all effective in prevention and treatment.

Normal lactation in the rat requires an adequate supply of choline. The young suckling rat shows defective growth and paralysis and a fatal issue may ensue when choline is absent from

the maternal diet. The necessity of choline for the growth of the chick, rat and dog, is attributed by McHenry and Patterson [165] not to any specific function, but to the requirement of choline for normal phosphatide formation which is so intimately concerned with fat transport.

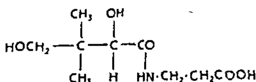
Acetylcholine Formation and Pharmacology of Choline

Choline exhibits actions closely similar to those of muscarine. Cardiac slowing, increased intestinal movements and increase of the salivary, lachrymal and other secretions are produced [178]. Herrmann [179] found that in old hens choline administration reduced the total cholesterol and cholesterol esters of the blood and also the levels of these substances in the aorta, heart, muscle and liver. He suggested that the cholesterol is mobilized from the blood and tissues of hens and metabolized under the influence of choline. Solandt [180] propounded the view that a deficiency of choline may be responsible for inadequate formation of acetylcholine. Solandt and Best [181] showed that a low dietary intake of choline was reflected in deficient vagal action and that lack of choline resulted in inadequate formation of acetylcholine at the nerve endings. Further investigation of this aspect is necessary. The therapeutic dose of choline approximates to the toxic one. Slowing of the heart rate and fall in blood pressure are dangerous effects.

PANTOTHENIC ACID

Pantothenic acid was known to be one of the 'bios' factors essential for the growth of yeast, and was subsequently identified as the chick antidermatitis factor [182, 183]. It was synthesized in 1939 [184], and an improved method of synthesis introduced the following year [185, 186]. The name is derived from the Greek meaning 'from everywhere', because of the ubiquitous distribution of the vitamin. Pantothenic acid is essential for the growth of certain bacteria [187].

Chemical Properties. – Pantothenic acid, $C_9H_{17}O_5N$, has the following graphic formula: –



The vitamin is available in the dextrorotatory form as a pale

yellow viscous oil, and, for therapeutic use as the dextrorotatory calcium salt, which occurs as fine white crystals of somewhat bitter taste, but devoid of any odour. The calcium salt is soluble in water, a stable solution resulting; some degree of solubility occurs in ether and amyl alcohol, but it is practically insoluble in other fat solvents. Destructive effects are exerted by alkalis, acids and dry heat. Pantoyltaurine is an analogue of the vitamin capable of inhibiting its action in a competitive nature.

Sources, Assay and Physiology. – Pantothenic acid is present in all types of animal tissues. Liver and kidneys are the richest animal sources, muscular tissues containing considerably smaller quantities. The royal jelly of the honey bee is the richest natural source. Synthesis occurs in green plants and in various moulds and bacteria. Yeast, eggs and cereals contain large amounts of the vitamin. The milling process removes considerable quantities of the essential nutrient. In its naturally occurring form, pantothenic acid is found in small proportion only as the free form, the greater part being bound to protein; proteolytic enzymes are necessary, to free completely the vitamin from animal tissues.

The assay of pantothenic acid content of food is determined in several ways, and the results expressed in units or, preferably, in micrograms. The yeast unit is a measure of the growth of yeast in the presence of the substance under examination as compared with its growth in a medium containing a standard dry rice bran extract. The chick unit involves the determination of the growth of the chick on a full diet devoid of pantothenic acid to which the material in question has been added. Microbiological methods are also employed; the number of organisms available for this purpose is very large, *Streptococcus lactis*, *Streptobacterium plantarum*, *Proteus morgani* and *Lactobacillus casei* being among those most extensively used.

It would not appear that the hydrochloric acid of the gastric juice is concerned to any great extent in the absorption of pantothenic acid. Meyer *et al.* [188] observed that patients suffering from pernicious anaemia showed a daily excretion of pantothenic acid slightly, but not significantly, less than that of normal subjects; similar conclusions were obtained following the oral administration of 100 mg. of calcium pantothenate. The vitamin is absorbed from ingested foodstuffs after it has been liberated from its protein bound form by the digestive processes

Urinary excretion of pantothenic acid has been measured in man. The content of the urine, collected over twenty-four hours, of 9 normal subjects showed a range from 1·46 mg. to 6·79 mg., with an average of 3·81 mg. [189]. Another investigation of this aspect demonstrated a mean daily urinary excretion of 3·42 mg.,

with a range from 1·10 mg. to 5·54 mg. in 29 medical students [190].

Within the body pantothenic acid undergoes partial destruction. Siegel *et al.* [191] estimated the pantothenic acid concentration of the blood of normal subjects, and found values between 19·7 and 33·6 micrograms per 100 c.c., and Stanbery *et al.* [192] obtained an average figure of 22·5 micrograms per 100 c.c. Patients with deficiency syndromes, such as beriberi, pellagra and ariboflavinosis, manifested a 25–50 per cent decrease in the blood levels and low urinary content of the vitamin [192]. Administration of the vitamin is followed by an elevation of the blood concentration which is usually sustained for less than twenty-four hours [193].

Deficiency States in Animals. – In rats, deficiency of pantothenic acid may result in haemorrhage, atrophy and necrosis of the adrenal glands [194]. Other features which may appear are dermatitis, greying of the hair, peculiar nasal exudate and renal and cardiac lesions. The nutritional achromotrichia has attracted considerable attention, and contradictory reports have been presented as to the efficacy of pantothenic acid in its prevention [195, 196]. So many different factors appear to be implicated in the greying process of the rat that the diverse results can only be explained on the basis of a complex aetiology, pantothenic-acid deficiency apparently being but one of the causal agents in its production. Pantothenic-acid-deficient rats show retardation or cessation of growth, the fur roughens and thins and a peculiar material collects on the hair and nose; this material exhibits a red fluorescence and contains a large amount of porphyrin [197]. Similar encrustations can be produced by partial dehydration in rats and Figge and Atkinson [198] consider that pantothenic acid may be involved in the regulation of water metabolism; the changes in the adrenal glands may be responsible for the alteration in water exchanges, and it has been demonstrated that vitamins are ineffective in curing the 'blood-caked whiskers' in rats if water be withheld [199]. Alopecia has also been described [200, 201].

Greying can be produced in mice by diets devoid of pantothenic acid. Although pantothenic acid may be curative, Woolley [202] demonstrated that inositol is also effective, and suggests that pantothenic acid acts in an indirect manner, occasioning intestinal synthesis of inositol. The position of para-aminobenzoic acid adds further to the complexity of the problem. Other pathological effects noted in mice subjected to a pantothenic-acid-deficiency-regime are dermatitis, alopecia, exudates around the eyes, spinal curvature, jerking movements of the hind-limbs, and degenerative changes in the nervous system [203, 204].

Dogs under similar conditions cease to grow and develop disturbances of the fat metabolism. Depression of the blood

cholesterol, cholesterol esters, lipoid phosphorus and total lipoids ensues. Loss of hair, rapid respiration and pulse rate, and severe gastro-intestinal symptoms have been observed. At post-mortem fatty changes in the liver, degenerative lesions in the kidney and reactive alterations of the gastro-intestinal tract are evident [205]. Pantothenic-acid supplementation alone was attended by persistence of a considerable degree of the hepatic pathology, whereas the combination of pantothenic acid and whole dried liver to the stock supplement resulted in only minimal liver damage [206].

The features of the syndrome in pigs are dermatitis, emaciation, a most extensive ulceration of the alimentary canal and loss of co-ordination resulting in characteristic 'goose-stepping' with the hind-legs [207, 208]. In the chick pantothenic-acid deficiency is succeeded by dermatitis, keratitis, spinal-cord lesions and fatty degeneration of the liver [209]. The hatchability of eggs is grossly impaired if pantothenic acid is excluded from the diet of the fowl [210].

Human Nutritional Studies. – Little is known about the fundamental action of pantothenic acid in the body. Williams [211] suggests that it is a component of some enzyme system which is essential for normal metabolism, and that it may be concerned with carbohydrate metabolism.

Reference has been made to the association of low blood levels of pantothenic acid in such conditions as pellagra [212]. An interesting feature in this connexion was the temporary elevation of the riboflavin concentration of the blood which followed an injection of pantothenic acid; the inter-relationship with riboflavin is further indicated by the transitory rise of the pantothenic acid content of the blood by 45 per cent succeeding an injection of riboflavin Gordon [213] reported pronounced improvement of 5 cases of peripheral neuritis with pantothenic acid therapy; 1 patient suffering from Korsakoff's syndrome and 2 cases of delirium tremens were similarly benefited The value of pantothenic acid in the syndrome of 'burning feet' is discussed later. In view of the greying of hair noted in experimental animals subjected to a diet devoid of the vitamin, pantothenic acid has been employed in the treatment of grey hair in humans. At this point it is only necessary to state that the available evidence is not in accord with any therapeutic effect in this direction

Pantothenic acid is a non-toxic substance, and 100 mg. have been injected intravenously in man without any untoward reactions [214]. The minimal requirements of man remain conjectural. Williams [215] assesses these at 10–12 mg. per day, whereas Grollman and Slaughter [178] refer to the daily allowances as between 3 and 4 mg.

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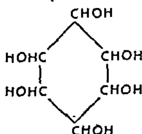
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INOSITOL

Eastcott [216] recovered a substance from tea which was found to act as a growth stimulant for yeast. This substance was accordingly included in the group of bios factors and was shown to be meso-inositol.

Chemistry. – Inositol is a crystalline substance. It is sweet-tasting and its formula is isomeric with d-glucose. Acids and alkalis exert but little deleterious effect. Inositol is soluble in water but not in alcohol or ether. In nature a number of isomers of inositol exist but these do not exert any vitamin activity. Meso-inositol occurs in nature in at least four forms – free inositol, phytin, lipositol and a water-soluble, non-dialysable complex [217]. Phytin is a calcium magnesium salt of inositol phosphoric acid and is the form chiefly found in plants. Inositol is a hexahydroxy cyclohexane with the following chemical structure: –



The biologically active form is meso-inositol which is optically inactive.

Sources. – Inositol is present in all plant and animal tissues. Within the body high values are found in muscle, brain, erythrocytes, heart and kidneys. The principal dietary sources are yeast, fresh fruits, vegetables, cereal grains, heart and brain. Cooking is associated with a loss of up to 50 per cent of inositol. Inositol is contained in certain phosphatides such as those of the tubercle bacillus and of the cephalin fraction of the brain and spinal cord [218]. Certain animals are capable of synthesizing inositol in the alimentary canal.

Estimation of Inositol. – Woolley [219] demonstrated that inositol was a stimulant for the growth of *Saccharomyces cerevisiae* and this offers a method for the determination of the vitamin. Other procedures have been advocated, but according to Woolley lack specificity or are too lengthy. Platt and Glock [220] devised a method which utilized the fact that inositol, like other glycols, reacts with periodate; the other naturally occurring glycols are eliminated beforehand.

Function of Inositol in Animals. – Little is as yet known of the

functions of inositol in man but animal studies have revealed that it has an essential rôle in nutrition. A peculiar disorder of dietary origin, curable by inositol, occurs in mice. Growth is retarded and abnormalities of the hair appear. The hair of the head, tail and of the legs below the knees remains unaffected, but loss of hair amounting at times to complete alopecia develops symmetrically in other parts of the body [221]. These changes were observed in only some 50 per cent of the animals. Woolley [222] subsequently revealed that mice can synthesize inositol and he demonstrated [223] the marked influence which the amount of pantothenic acid present in the diet exerted over the appearance of the inositol-deficiency state. When pantothenic acid was simultaneously restricted, the inositol-deficiency syndrome could readily be produced, whereas it arose in only a few instances when pantothenic acid was simultaneously administered in large doses. Inositol is concerned in the 'spectacled-eye' condition of rats. In addition to the relationship with pantothenic acid, inositol and para-aminobenzoic acid show certain inter-relationships. According to Martin [224] inositol increases the growth of certain intestinal organisms which utilize a member of the vitamin-B complex, known or unknown, and so sets up a deficiency of that particular factor; on the other hand, para-aminobenzoic acid enhances the growth of another set of bacteria which absorb inositol and an inositol-deficiency state is precipitated. The complexity of the inter-relationships of the components of the vitamin-B complex is further demonstrated by the protective influence of inositol on the fatty liver of rats produced by feeding with biotin [225, 226] Inositol has a lipotropic function and is beneficial in conditions of fatty livers in rats produced by other means than biotin. Inositol is essential for the growth of cotton rats, guinea-pigs, hamsters and chickens.

Inositol inhibits the tumour growth in mice transplanted with sarcoma 180. Inositol was given by intravenous injection and the response was proportional to the dose.

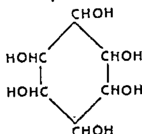
Inositol in Human Nutrition

There is as yet little knowledge concerning this aspect or of the normal requirements of man. Inositol may have a lipotropic activity in man [227] and its value in skin diseases has been suggested. Animal studies indicated an ability of inositol to stimulate peristalsis. Twenty patients suffering from constipation were given inositol and in none was any change in the normal bowel habits noted [228]. No effect from inositol administration was obtained in alopecia in human beings. Doses of 1 to 2 grams by mouth were non-toxic to man.

INOSITOL

Eastcott [216] recovered a substance from tea which was found to act as a growth stimulant for yeast. This substance was accordingly included in the group of bios factors and was shown to be meso-inositol.

Chemistry. – Inositol is a crystalline substance. It is sweet-tasting and its formula is isomeric with d-glucose. Acids and alkalis exert but little deleterious effect. Inositol is soluble in water but not in alcohol or ether. In nature a number of isomers of inositol exist but these do not exert any vitamin activity. Meso-inositol occurs in nature in at least four forms – free inositol, phytin, lipositol and a water-soluble, non-dialysable complex [217]. Phytin is a calcium magnesium salt of inositol phosphoric acid and is the form chiefly found in plants. Inositol is a hexahydroxy cyclohexane with the following chemical structure: –



The biologically active form is meso-inositol which is optically inactive.

Sources. – Inositol is present in all plant and animal tissues. Within the body high values are found in muscle, brain, erythrocytes, heart and kidneys. The principal dietary sources are yeast, fresh fruits, vegetables, cereal grains, heart and brain. Cooking is associated with a loss of up to 50 per cent of inositol. Inositol is contained in certain phosphatides such as those of the tubercle bacillus and of the cephalin fraction of the brain and spinal cord [218]. Certain animals are capable of synthesizing inositol in the alimentary canal.

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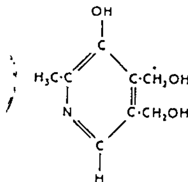
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PYRIDOXINE

Pyridoxine (vitamin B_6) was recognized in 1934 as being implicated in the production of acrodynia in rats [229]. György applied the designation 'vitamin B_6' but the name pyridoxine was suggested in view of the pyridine nucleus in the molecule. Pyridoxine was isolated in 1938.

Chemistry. – Pyridoxine is a white crystalline powder with a slightly bitter taste. Like nicotinic acid the basic structure is the pyridine ring. The structural formula is



Pyridoxine is very soluble in water and in alcohol. It is destroyed by light but resists heat and alkali and acid. An orange-yellow colour is produced by the action of ferric chloride. Pyridoxal and pyridoxamine are among other naturally occurring forms of the vitamin. Pyridoxal is the 4-aldehyde of pyridoxine and pyridoxamine is obtained by amination; they are almost as biologically active as pyridoxine for higher animals but much variation in the capacity of micro-organisms to utilize these substances exists.

Sources. – Pyridoxine is contained in a wide variety of foodstuffs. Yeast, liver, muscle, fish, seeds, legumes, wheat germ and rice polishings offer rich sources but little is found in milk, fruits and vegetables.

Estimation of Pyridoxine. – The rat assay method affords a reliable means of estimation and depends on the cure of rat acrodynia. Microbiological methods are complicated by the different growth responses of various bacteria to the different naturally occurring pyridoxine substances but a satisfactory procedure is measurement against *Saccharomyces carlsbergensis.* Chemical methods include the use of ferric chloride and diazonium salts.

Function of Pyridoxine in Animals. – In rats, pyridoxine deficiency results in acrodynia. Oedema, swelling and denuding of the paws develop in the initial stages and then the tips of the ears, nose and areas about the mouth become involved; the remaining portions of the body may be affected [230]. Not all the rats subjected to a

diet deficient in pyridoxine develop the dermatitis [231] and pantothenic acid and the essential fatty acids are concerned in the cure or prevention of the disorder [232, 230]. Retardation of growth in the absence of any dermatitis may be produced in rats maintained on a diet deficient in vitamin B_6 [233].

A microcytic hypochromic anaemia appears in dogs on a diet deficient in pyridoxine [234] and in these animals and in rats and pigs convulsions may occur [235] Pyridoxine administration effects a rapid restoration of the blood picture to normal. Convulsive movements are also reported in chicks under conditions of pyridoxine deficiency and there are retardation of growth, anaemia and other nervous manifestations [236]. Prolonged lack of pyridoxine may lead to a fatty infiltration of the liver.

A yellow compound can be recovered from the urine of pyridoxine-deficient rats, and has been identified as xanthurenic acid. This compound originates from the tryptophane of the diet [237]. Pyridoxine would appear to be essential for the normal metabolism of protein Signs of pyridoxine deficiency in rats could be accelerated in their onset by the inclusion of large amounts of protein in the diet [238] It would appear that certain derivatives of pyridoxine function as a co-enzyme in the de-carboxylation of tyrosine, arginine, ornithine, glutamic acid and diphenylalanine. McHenry and Gavin [239] suggested that pyridoxine might be necessary for the synthesis of fat from protein in rats.

Excessive doses of pyridoxine are toxic. Doses above 1 gram per kilo of body-weight produced toxic convulsions and impairment of co-ordination in animals; this dose is at least 1,000 times the therapeutic dose [240] Intestinal biosynthesis of pyridoxine takes place in some animals.

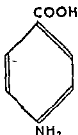
Pyridoxine in Human Studies

There is little information regarding the function, requirements or physiology of vitamin B_6 in the human body. Additional improvement has been reported following its use in pellagra and oral lesions of deficiency syndromes may yield to administration of the vitamin. Pyridoxine has been used in blood, neurological and dermatological disorders and its value in these is discussed under the various sections. Although it is not definite that pyridoxine is essential for normal human nutrition, as judged from animal experiments, the human requirement is about 2 mg. per day.

PARA-AMINOBENZOIC ACID

Para-aminobenzoic acid was synthesized in 1863 [241]. It

crystallizes in colourless needles which change to a yellowish hue on aging. It is soluble in water and to a greater extent in alcohol. The chemical structure is



Sources and Assay. – Most tissues contain para-aminobenzoic acid. Yeast, liver, wheat germ, rice polishings and whole wheat offer good sources of supply. The growth of different organisms has been utilized in the estimation of the concentration of the vitamin, as has the measurement of the degree of inhibition produced by para-aminobenzoic acid on the bacteriostatic action of sulphonamides. Landy and Dicken [242] described a satisfactory method employing the growth response of *Acetobacter suboxydans*. Chemical methods are not satisfactory.

Action of Para-Aminobenzoic Acid

Para-aminobenzoic acid is necessary for the growth of chicks [243] but the possibility has been raised that this function is an indirect one obtained by a stimulating effect on the intestinal flora. The black or piebald rat maintained on a diet deficient in this substance develops greying of the hair, which effect was claimed by Ansbacher to establish the vitamin status of the compound. A series of experiments demonstrated the vitamin to be essential for normal lactation in the rat. Synthesis of para-aminobenzoic acid occurs in the alimentary canal of some animals. Much remains to be learned of the inter-relationships of the various members of the vitamin-B complex. Some references to these are made elsewhere. It is not yet possible to present a clear picture and the fact that para-aminobenzoic acid is present in the structure of pteroylglutamic acid has further complicated the picture, since a possibility is that, in part at least, the action of the former vitamin may be attributable to an enhanced biosynthesis of the latter.

Para-aminobenzoic acid modifies the formation of melanin. It prevents greying in rats produced by hydroquinone administration. Achromotrichia in animals has been reported to yield to pantothenic acid, biotin, pteroylglutamic acid or para-aminobenzoic

See Addendum to this page at end of book.

acid; the importance of each is difficult to assess and their interactions and influence on the intestinal flora remain to be gauged.

Para-aminobenzoic acid is an essential metabolite for micro-organisms. It antagonizes the bacteriostatic action of the sulphonamides. The vitamin has been reputed to protect against the toxic effects of arsenical compounds but clinical studies have not proved its value in this respect in man. In large doses it is toxic to animals [244].

Strauss *et al.* [245] demonstrated that following the ingestion of 1 to 4 grams of para-aminobenzoic acid the blood level of the substance reached a maximum in one to two hours. Para-aminobenzoic acid is rapidly conjugated and the free form could not be found in the blood four hours after the administration of 2 grams. After twelve hours almost complete recovery from the urine was obtained. Strauss and Finland [246] observed no toxic effects after the administration of massive doses of the compound to human beings. As a therapeutic agent, para-aminobenzoic acid has been used chiefly in dermatological lesions and this aspect and its relationship to sulphonamide drugs are discussed under the respective sections.

FOLIC ACID

The investigations, which have proceeded in the elucidation of knowledge of the haematopoietic factors of the vitamin-B complex, have yielded a number of factors whose relationship and identity are not yet completely understood. The subject has been reviewed by Berry and Spies [247]. Certain aspects of the somewhat unwieldy literature on the subject will be presented.

Lactobacillus casei requires extracts of plant or animal origin in addition to riboflavin, nicotinic acid, pantothenic acid, pyridoxine and tryptophane for growth on a purified hydrolysed casein medium. Snell and Peterson [248] demonstrated that liver and yeast were rich sources of the essential growth factor. Treatment of the extracts with norite in acid solution and elution of the adsorbate with pyridine-alcohol solutions produced two fractions – the norite eluate factor and the norite filtrate factor, the activity of the latter subsequently being shown to depend on its content of pyridoxine and biotin. A lactobacillus factor was prepared from liver by Stokstad [249] and is identical with the norite eluate factor of Snell and Peterson; their effect on the growth of *L. casei* is equal to that on *Streptococcus lactis R.* Isolation and synthesis of the compound has been achieved [250, 251] and the designation pteroylglutamic acid has been applied. Hutchings *et al.* [252] discovered that the norite eluate factor contained a chick growth

factor. The term 'folic acid' was introduced by Mitchell, Snell and Williams [253] to indicate a substance obtained from spinach which was active in stimulating the growth of *S. lactis R.* Little significant differences were found between this substance and the two factors previously described and what differences existed might be explained by the lack of purity of the various fractions examined. Folic acid was found to have equally stimulating effects on the growth of *L. casei* and *S. lactis R.*

Keresztesy and his co-workers [254] reported the isolation of an SLR factor which was highly potent in stimulating the growth of *S. lactis R* but possessed little activity in this direction for *L. casei.* Stokstad [255] extracted a factor from yeast which showed but half the stimulating growth effect for *S. lactis R* as for *L. casei* and Hutchings *et al.* [256] reported the isolation of the 'fermentation factor' which they claimed to be distinct from pteroylglutamic acid as determined by spectroscopic studies. The activity of this substance is probably due to pteroyltriglutamic acid; it contains two more glutamic-acid groups than pteroylglutamic acid. The SLR factor of Keresztesy *et al.* may be due to pteroic acid.

When monkeys are fed a diet similar to that of the poorer classes of Bombay a hyperchromic macrocytic anaemia develops [257]. The anaemia is curable by treatment with crude liver extract administered orally or parenterally. This property could also be demonstrated in yeast, marmite and wheat germ. Day *et al.* [258] by means of a special diet fed to monkeys produced a syndrome characterized by progressive anaemia, leucopenia, thrombocytopenia, lesions of the oral cavity and diarrhoea; lowered resistance to infection was present and bacillary dysentery was of frequent occurrence. The blood picture might bear a close resemblance to that of pernicious anaemia in man and Day *et al.* [259], who observed normocytic types of anaemia in the majority of animals, stressed the fact that the anaemia was not hypochromic, microcytic in type. Marked variations in the blood state were evident and a profound fall in the leucocyte count might appear in the absence of any pronounced anaemia. Crude liver extract and yeast could promote recovery
cytopenia. The name vitamin M
of curing this syndrome which
deficiency or nutritional cytopenia. It was later demonstrated that addition of folic acid concentrates to the diet effected a similar response [260]. Vitamin M would appear to be identical with pteroylglutamic acid.

Hogan and Parrott [261] reported the development of anaemia and retardation of growth in chicks subsisting on a synthetic diet. They gave the name vitamin B_c to the member of the vitamin-B-

complex, deficiency of which they considered to be responsible for the syndrome. A concentrate of the norite eluate factor was found to be effective [262] as was synthetic *L. casei* factor from liver [263]. While yeast extracts offered a rich source of chick anti-anaemia compounds their microbiological activity for *L. casei* was slight and it was considered that vitamin B_c is held in conjugated form in yeast (vitamin-B_c conjugate) and is liberated by an enzyme (vitamin-B_c conjugase) [264]. Vitamin B_c conjugase is demonstrable in most tissues of the body and inhibitors of its action are also present in crude tissue extracts. Vitamin B_c conjugate yields 7 moles of glutamic acid and is pteroylheptaglutamic acid.

Briggs *et al* [265] discovered two dietary factors which they considered distinct from folic acid – vitamin B_{10} and vitamin B_{11}; the former was essential for feather development and the latter for growth in the chick and both factors were capable of preventing the onset of anaemia. The activity of vitamin B_{10} and vitamin B_{11} is due to folic acid [266].

Xanthopterin, the yellow pigment of butterfly wings, was so named by Wieland and Schopf [267]. A pigment present in the urine and known as uropterin has been proved to be xanthopterin [268]. It is ineffective in correcting the anaemia of vitamin-B_c-deficient chicks but is active against the vitamin-M-deficient anaemia of monkeys [269]. Chemically it is related to pteroylglutamic acid.

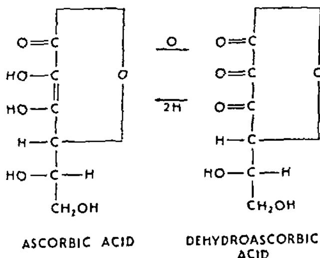
There is a factor present in yeast and liver essential for normal hatchability of eggs Schumacher *et al.* [270] recognized two components – factors R and S. The factor U of Stokstad and Manning [271] is required for the growth of the chick. All three substances have similarities in chemical structure to folic acid.

Pteroylglutamic Acid – Pteroylglutamic acid was synthesized by Angier and his collaborators [272]. It is a bright yellow crystalline substance in contrast to the colourless compounds of the liver preparations effective in pernicious anaemia, and it is not identical with the active liver principle. It is distinguished from the extrinsic factor since its action is not dependent on the presence of gastric juice, and it cannot be the intrinsic factor for it is active on parenteral administration [273]. The amount of folic acid which can be obtained from liver extracts is of too small an order to explain their haematopoietic properties Stokstad and Jukes [274] observed that *L. casei* factor was not liberated in appreciable quantities from concentrated liver extract by treatment with vitamin B_c conjugase. During the elaboration of animal experimental studies the term 'folic acid' came to be employed in reference to different compounds From the clinical aspect it is now employed to denote the synthetic commercial preparations and while

VITAMIN C

SYNONYMS FOR vitamin C are ascorbic acid, cevitamic acid and anti-scorbutic vitamin. The designation 'ascorbic acid' was suggested by Szent-György and Haworth [285] to indicate its action against scurvy. The American Medical Association introduced 'cevitamic acid' in the nomenclature but abandoned the term in 1939. *Vitamin C was isolated and identified in 1932* [286] and its synthesis was effected in the following year [287].

Chemical Properties. – Vitamin C is a white crystalline substance with a taste similar to that of citric acid. It is soluble in water and in alcohol but insoluble in fats and fat solvents. Ascorbic acid, $C_6H_8O_6$, is chemically related to the sugars and shows optical activity, the laevo form being the vitamin while the dextro compound is inactive against scurvy. Vitamin C shows no great degree of stability and is readily oxidized to dehydro-ascorbic acid; the reaction is an easily reversible one, so that dehydro-ascorbic acid may be reconverted to ascorbic acid. The graphic formulae are as follows: –



Dehydro-ascorbic acid is biologically equivalent to l-ascorbic acid, since its reduction to the latter substance is readily obtained in the tissues. Further oxidation of dehydro-ascorbic acid to diketogulonic acid and then to oxalic acid and l-threonic acid is associated with loss of antiscorbutic activity; degradation of dehydro-ascorbic acid is an irreversible process and in the body it is probably protected against these changes by reduction to ascorbic acid, the protective agent apparently being glutathione.

currants contain considerably greater quantities than the citrus fruits. The content of various fruits shows marked fluctuations, but apples, bananas, pears and stone fruits generally contain only small amounts of vitamin C. Jams reflect the ascorbic acid content of the substances from which they have been prepared and while retaining the greatest part of the vitamin content, the dilution with water and sugar reduces the vitamin concentration. Green leafy vegetables are important sources of the vitamin. Dairy products offer negligible quantities. Dry seeds and cereals are devoid of ascorbic acid which is formed when germination occurs. In the higher plants considerable quantities are recoverable from those parts demonstrating active growth – the roots, stems, buds and pods. Much variation is found in the amount of vitamin C present in different varieties of vegetables and fruits, and this is further influenced by the nature of the soil, the season of the year, the activity of growth and the amount of sunshine to which the growing article has been exposed.

Synthesis of ascorbic acid occurs in the plant kingdom, compounds of similar chemical nature probably being used in the process. Storage exerts a deleterious effect on the vitamin-C content of vegetables and fruits; after several days there may be a loss of some 50 per cent. Another detrimental influence is bruising and crushing which liberate oxidases contained in the fruits and vegetables, these oxidases rapidly catalysing the oxidation of the ascorbic acid by the atmospheric oxygen. *In vitro* tests demonstrated that ascorbic acid oxidase in a period of six hours at body temperature resulted in loss of approximately 60 per cent of the vitamin [290]. Cold storage, however, provides a satisfactory means of preserving the vitamin-C content of foodstuffs. Since vitamin C exists in all living tissues the animal kingdom provides a means of its supply although this is not commensurate with that obtained from the plant kingdom. Fresh meat does contain fair amounts, but these are greatly reduced after hanging. Organs with a high degree of metabolic activity show the largest content of ascorbic acid and among these are the suprarenals, liver and the thyroid.

Assay and Estimation of Vitamin C. – Spectroscopic and polarographic methods have been employed as have biological, but chemical procedures are simple and are those commonly used today. Vitamin C is oxidized by 2 : 6 dichloro-phenol-indophenol which possesses a blue colour, the colour disappearing as the compound is reduced. The dye oxidizes many compounds besides ascorbic acid and does not measure the dehydro-ascorbic acid content. The latter substance may be converted by hydrogen sulphide to ascorbic acid and various modifications have been introduced to make allowances for the other reducing compounds, a useful method being the addition of 20 per cent hydrochloric

acid in which solution vitamin C no longer decolorizes the dye [291]. Vitamin C reacts immediately with 2 : 6 dichloro-phenol-indophenol whereas the other biologically occurring substances capable of reducing the dye (such as thiosulphate, cysteine, riboflavin and nicotinic acid derivatives) do so at a much slower rate. In acid solution 2 : 6 dichloro-phenol-indophenol presents a red colour and the titration is best conducted at pH 4. Because of the rapidity of oxidation of ascorbic acid by atmospheric oxygen, the material under examination should be analysed as soon as possible and, if the estimation be delayed, the addition of glacial acetic acid and storage in a dark stoppered container will retard the oxidative changes.

Methylene-blue is the other chemical in frequent use for vitamin-C computation; the vitamin discharges the blue colour. It is a very sensitive indicator of the ascorbic-acid content. There are many additional chemical quantitative measures which have been suggested, but they are not frequently employed.

VITAMIN-C REQUIREMENTS OF ADULTS

Many of the controversial points on the vitamin-C requirements of man arise from the different criteria utilized for this estimation. Pijoan and Lozner [292] point out that four levels of the tissue reserves may be recognized. The lowest level is that at which scorbutic symptoms appear and above this there is the protective minimum, no clinical evidence of scurvy existing, but the body is maintained just above the overtly deficient zone The third is a wide field allowing of tissue storage and finally there is the state of tissue saturation They assess the daily intake in respect to the various levels as respectively under 20 mg , 20-30 mg., 30-75 mg., and 75-100 mg. of vitamin C Intakes above the last figures provide a needless excess. The term 'saturation' implies a condition in which the body reserves are at a theoretical optimum; there is a wide margin of the body reserves between this state and conditions of well-being which are not enhanced by administration of increased amounts of the vitamin Investigations of apparently healthy individuals have shown a wide prevalence of vitamin-C undersaturation, and the question at issue resolves itself into the determination of whether man's allowances are to be based on the maintenance of tissue saturation or on a state of health which is not improved by supplements of the vitamin.

The [illegible] Council of the [illegible] 75 mg. for the [illegible] t female (123 lb. weight). A similar conclusion was reached by Kyphos and

See Addendum to this page at end of book

his co-workers [293], while Ralli and Sherry [294] state that the optimum allowance should be 100 mg. daily. Much smaller intakes are consumed, however, with no obvious evidence of deleterious effects. Estimations of the average daily vitamin-C intakes of the personnel of the three British military services revealed figures of 30 mg. and under [295, 296, 297]. Najjar *et al.* [298] stated that scurvy does not develop on a daily consumption of 18–25 mg. of ascorbic acid, and Pijoan and Lozner [292] found that if tissue saturation were obtained every four months of the year protection would be afforded against scurvy, this procedure requiring approximately 2 grams of the vitamin in divided doses during the period of saturation and representing a daily intake of about 22 mg.

It is obvious that the period required for the development of the scorbutic syndrome will vary with the tissue reserves of the vitamin, and it is recognized that under certain adverse conditions the requirements of ascorbic acid are increased, and, accordingly, the safe practice would be to ensure an adequate storage in the event of circumstances of diminished dietary intake and of these adverse influences. Tissue saturation in itself would appear merely to widen the margin of safety and is perhaps an unnecessarily high standard; but tissue reserves should be maintained at adequately high levels and for this purpose a reasonable estimation of the daily requirements would appear to lie between 50 and 75 mg. of vitamin C. For the maintainance of health itself, however, much smaller amounts will suffice and these, as shown above, lie below the level of 30 mg. per day. Lowry *et al.* [299] estimated that the normal adult contains about 4 grams of vitamin C in the tissues.

Infections, both acute and chronic, raise the requirements of vitamin C. Among them are pneumonia, rheumatic fever, rheumatoid arthritis, the specific infectious diseases and tuberculosis. It is not the mere presence of fever which is the responsible agent [300]. Increased metabolic activity is associated with greater demands of the vitamin. Hyperthyroidism, the administration of thyroid in therapy and malignant disease are examples. The sum of existing evidence would appear to negate the necessity for an increased allowance of vitamin C in those undergoing strenuous exercise, nor do climatic conditions influence the requirements. An interesting aspect is the increased urinary excretion of ascorbic acid which follows the administration of certain drugs and for which allowance should be made. Aspirin, salicylates, the barbiturate series, sulphonamides, adrenalin and the oestroform compounds are among the important members. Ether and chloroform exhibit a similar activity. Scurvy was a not infrequent event in soldiers suffering from dysentery during the first World War; it has

been shown that large quantities of vitamin C may be lost in those affected with diarrhoea [301].

Metabolism of Vitamin C. – Ascorbic acid is absorbed chiefly from the small intestine passing into the blood stream. Satisfactory demonstration of any destruction of vitamin C in the alimentary tract is not yet available. No evidence was found for the occurrence of loss of vitamin C in the digestive tract by the activity of the ascorbic-acid oxidases of ingested vegetables [302]. Achlorhydria would seem to retard the rate of absorption, the plasma levels of those with absence of gastric hydrochloric acid usually being at lower levels than normal. Storage of ascorbic acid occurs in the tissues and the concentrations present in different organs depends on the metabolic activity; those tissues with a high metabolism have a high vitamin-C content. Yavorsky *et al.* [303] found a decreasing concentration of vitamin C in the organs in the following order: pituitary gland, corpus luteum, adrenal cortex, young thymus, liver, brain, testis, ovary, spleen, thyroid, pancreas, salivary glands, lung, kidney, intestinal wall, heart and muscle. The tissues of younger animals are richer in ascorbic acid than those of older animals. The amount present in the cerebrospinal fluid parallels that of the plasma and fluctuates with the dietary intake.

Excretion of vitamin C takes place in the faeces and urine. Faecal excretion has been estimated at not more than 6 to 10 mg. per day even when large amounts are ingested [304, 305]; this small excretion does not hold when gastro-intestinal disorders exist. Ascorbic acid may be found in the urine as such or as dehydroascorbic acid Renal excretion involves glomerular filtration and tubular resorption The latter mechanism is limited to a maximum rate and, when this is unable to keep pace with the quantities presented to the tubules, the excess appears in the urine; should the quantities be below the maximum rate, the urinary excretion falls but even at the lowest plasma levels the reabsorption of the vitamin is never complete and there is a minimum amount excreted in the urine [306, 307]. The renal threshold for vitamin C determines the concentration of plasma ascorbic acid for the particular person; those with high renal thresholds will waste less vitamin C than others with low renal thresholds. Faulkner and Taylor [308] considered that the critical level of excretion of vitamin C was in the region of 1·4 mg per cent and Goldsmith and Ellinger [309] concurred with this figure Lewis *et al.* [310] observed the renal threshold to range between 1·1 and 1·8 mg. per cent. As the intake of vitamin C diminishes, so there is a decrease in the urinary excretion. During a state of body depletion administration of the vitamin results first in the replenishment of the tissue reserves. Kyphos *et al.* [311] reported that doses of vitamin C as high as

1·5 grams in one day, were followed by no significant renal loss if the plasma levels were low in ascorbic-acid-deficient patients. The total amount of ascorbic acid required to produce a twenty-four-hour excretion of 40 mg. or more varied from 0·5 to 2·0 grams. These investigators considered that there was a wide range of renal threshold and obtained in their series values for this between 1·1 and 1·9 mg. per cent. It was noted that patients with blood dyscrasias and renal impairment responded atypically to ascorbic acid treatment. Sendroy and Miller [312] also indicated that low urinary excretion of vitamin C in nephritic subjects did not necessarily indicate a low ascorbic-acid content of the blood.

The Function of Vitamin C. – Vitamin C can be synthesized by all animals studied except the guinea-pig, man and other primates and possibly certain ungulates. There are a few suggestive inferences that under certain conditions man can manufacture the vitamin endogenously but the evidence for this process is as yet inconclusive.

The validity of the participation of ascorbic acid in specific enzyme reactions concerned with tissue respiration has not been satisfactorily established. Vitamin C is essential for the formation and maintenance of the intercellular substance and a pure deficiency produces morphological changes which are largely restricted to supporting tissues of mesenchymal origin [313]. Failure of formation and maintenance of the intercellular materials ensues. All intercellular substances of the supporting tissues (bone, cartilage, fibrous connective tissue and dentine) have a common substructure of collagen, and Wolbach and Bessey indicate that it is this protein substructure which is not produced, or is produced in defective form. The most constant pathological finding in scurvy is atrophy of the connective tissue. Wolbach *et al.* [314, 315] state that the fibroblast normally lies in an amorphous ground substance in which fibrils are formed and collect together as wavy bands of collagen. These fibrils are cemented together by a translucent matrix and vitamin C is essential for this phase. They consider that there is no abnormality in the fibroblasts or in the ground substance, but the formation of the intercellular material is defective. Weakness of the bone, cartilage, capillaries and other structures results and the reparative processes cease or are impaired. Another theory of the interpretation of the action of vitamin C is that the vitamin is necessary for the normal function and structure of the fibroblast and osteoblast and that, in the absence of the vitamin, the products of the activity of these cells – collagen and bone – are imperfect.

Tests for Detection of Vitamin-C Deficiency

(1) *Vitamin-C Levels in the Blood.* – Vitamin C is not equally

distributed among the various elements of the blood. The concentration in the erythrocytes is always lower than that of the white cell-platelet layer. In the latter the highest concentration of ascorbic acid is found; normally this is 20 to 40 times that of the plasma concentration and the red cell levels are 1 to 2·5 times greater than that of the plasma [316]. A rapid diffusion of ascorbic acid takes place from the plasma into the leucocytes, whereas this process occurs at a slow rate into the erythrocytes. In states of vitamin-C depletion the plasma shows the earliest evidence of lowering of the vitamin-C content, while the white cell are the last to be depleted. Chevillard and Hamon [317] investigated the ascorbic-acid content of the blood plasma, red cells, leucocytes, platelets, lymphatic ganglia and bone-marrow in the guinea-pig, and concluded that the most sensitive index of changes in the vitamin-C nutrition was the ascorbic-acid concentration of the leucocytes and blood platelets A natural surmise might be that estimations conducted on the whole blood would afford the most satisfactory results, but beside the technical difficulties, fluctuations in the white cell count, as in leukaemia, leucocytosis and granulopenia, tend to invalidate the readings Haemolysis is an important factor and decreases the estimated concentration of vitamin C in the plasma

Claims have been put forward for the validity of the plasma-vitamin-C concentration as an indication of a deficiency state, These have been criticized, and it is generally agreed that low plasma levels in themselves do not provide a reliable measure either of vitamin-C deficiency or of the degree of tissue unsaturation, although a value of 0·7 mg. per cent or higher in the fasting specimen usually reflects a satisfactory state of ascorbic-acid nutrition. Low or zero values have been obtained in the plasma in subjects with no evidence of vitamin-C deficiency. The renal threshold will also influence the height of the plasma ascorbic acid which may be lowered if the former is set at a low concentration. Normal plasma-ascorbic-acid concentrations may range between 0·6 and 2·5 mg. per 100 c c Johnstone *et al.* [318], however, found the fasting values of 372 young healthy Canadians below 0·6 mg. per 100 c.c. in 55 per cent and below 0·25 mg. in 19 per cent; a great change in the intake of ascorbic acid was found to be accompanied by changes in the fasting blood-plasma values in one to two weeks.

(2) *Intradermal Tests.* – These are based on the injection intradermally of a dye substance which can be decolorized by the action of vitamin C, the rate of decolorization varying directly with the tissue concentration of the vitamin. Rotter [319] introduced the procedure. He employed 0·01 c.c. of an N/400 solution of 2 : 6

dichlorophenol-indophenol and raised a blue wheal in the skin of about 2 mm. in diameter; disappearance of the colour within five minutes was considered to indicate tissue saturation, a period of five to ten minutes a normal amount of ascorbic acid in the tissues, and a reduction time of more than ten minutes, evidence of a vitamin-C-deficiency state. There has been much diversity of opinion concerning the value of this test. Portnoy and Wilkinson [320] and Reddy and Sastry [321] found good correlation between the test and blood-ascorbic-acid levels, but others [322, 323, 324] failed to observe any parallelism between the two measurements. Wright and MacLenathen [325] reported that there existed such wide fluctuations of the results in the same individual as to prevent the formulation of a normal range. Slobody [326] claimed reliability for a modification of the original method. A more concentrated solution of the dye – N/300 – was used and a wheal of 4 mm. in diameter was raised; a time of more than fourteen minutes for the disappearance of the colour was reckoned to signify a definite degree of tissue undersaturation, from nine to thirteen minutes mild undersaturation and less than nine minutes a normal vitamin-C content in the body. Certain local factors which are difficult to control influence the readings, an example being the local vasomotor state. The actual site of the injection is also a modifying agency and defects in the technique may provide erroneous readings. Methylene-blue has also been utilized for intradermal injection procedures.

(3) *Urinary Excretion Studies.* – Under ordinary circumstances normal individuals will excrete in the region of 20 mg. of ascorbic acid per day in the urine. It is necessary to avoid loss of the excretory products of vitamin C (ascorbic acid and dehydro-ascorbic acid) in the collected urine. Glucose and protein have no effect in this direction. The estimation will give unsatisfactory results unless due precautions are taken. The addition of 8-hydroxyquinone and 5-N sulphuric acid to the urine and storage in the cold have been advised [327, 328]; Holmes and Campbell [329] suggest the addition of 50 c.c. glacial acetic acid, and 3 grams of calcium carbonate and a fragment of marble to the dark container used for the collection of the specimens. The result of the estimations of the vitamin C in the twenty-four-hour urinary excretion may give an unreliable picture of the tissue reserves, since small amounts may be excreted by individuals whose stores are not much reduced below complete saturation. Richter and Croft [330] point out that while the results of estimation of urinary ascorbic acid by the dichloro-phenol-indophenol method is sufficiently accurate at high ascorbic-acid levels, the results obtained at low vitamin-C levels are unreliable; thiosulphates are among the substances which

interfere with the accuracy of the readings and they suggest that lead acetate be added to precipitate the thiosulphate present.

Saturation tests have been devised in an attempt to estimate the quantities of vitamin C necessary to obtain saturation of the tissue storage of the vitamin. The tissue reserves will determine the urinary excretion following the administration of a test dose of ascorbic acid; a low urinary excretion of the vitamin is an expression of depleted body reserves and vice versa. The oral method described by Harris and Abbasy [331] affords a simple procedure for conducting this form of investigation. After the patient has emptied his bladder at 9 a.m., the urine passed between then and 12 a.m. is collected and the concentration of vitamin C measured by the 2 : 6 dichloro-phenol-indophenol method. This procedure is repeated for the next two days, after which the test dose (700 mg of vitamin C per 10 stone of body-weight) is given at 10 a.m. each morning, until the vitamin-C content of the urine voided between 2 p.m. and 5 p.m. is equal to or greater than 50 mg. per 10 stone of body-weight The number of days required to effect this level of urinary ascorbic-acid output is a measure of the tissue reserves. The actual quantity of vitamin C necessary to saturate the body is obtained by multiplying this figure by the test dose. Modifications and criticisms are based on the amount of ascorbic acid which should be contained in the test dose, the most satisfactory period for the collection of the urine and the quantity of urinary vitamin C which signifies tissue saturation.

Saturation tests may also be carried out when the test dose is administered by the parenteral route. Again several different procedures have been described. Ralli *et al* [332] inject 100 mg. of vitamin C intravenously and consider that an excretion of 40 mg. or more in the urine during the first three hours signifies tissue saturation Wright [333] employs 1,000 mg. of ascorbic acid by the intravenous route and regards a urinary excretion of 400 mg. within five hours of the administration of the test dose, as normal. It is doubtful whether subjection of the patient to an injection is justifiable in conditions other than those which interfere with normal absorption of the vitamin.

The vitamin C administered will show a delayed appearance in the urine in the presence of renal dysfunction A decreased output may also be an expression of greater utilization of the ascorbic acid, rather than of tissue undersaturation. A further factor which influences interpretation of the saturation tests is that the content of vitamin C in the urine when man is consuming an ordinary diet, may fluctuate during the course of the day; this may well produce differences in the figures obtained from the estimation of the ascorbic-acid content of the urine collected for a

Heinemann [342] who obtained no decrease in capillary fragility after saturation of the tissues with ascorbic acid had been obtained. These and other similar reports would appear to detract from the value of the test as an index of vitamin-C nutrition. Furthermore there exist a number of modifying factors which render the results open to question; among these are the site of the skin examined, the thickness and vascularity of the skin, and the age of the patient. An interesting observation was made by Scarborough [343, 344] who discovered an increased capillary fragility following surgical operations, internal injuries, the intramuscular injection of as little as 4 c.c. of blood or the experimental injection of blood into the upper or lower ends of the alimentary tract. It is possible that the escape of blood into the extravascular tissues in scurvy may enhance any tendency to capillary fragility by a similar mechanism, the nature of which is not as yet apparent.

Pathology of Vitamin-C-Deficiency States

According to the proponents of the 'gelation' theory, absence of vitamin C affects the physical character of the intercellular substance which is then maintained in a fluid state. Addition of the vitamin alters this state to that of a gel The alternative view, as has been stated, is that the fibroblasts and osteoblasts are directly affected. Whichever theory is correct, haemorrhages from the capillaries are characteristic of avitaminosis C and these haemorrhages may appear in the skin, mucous membranes or internal organs. Their site is largely determined by local stress and their size shows wide variation. Perifollicular haemorrhages are especially a feature of the syndrome as is the subperiosteal effusion of blood found in the younger age-groups. Calcification of a haematoma may occur. In the skeletal structures the effects of scurvy are manifested particularly in the ends of the growing long bones. The osteoblasts alter in shape and assume an appearance resembling that of fibroblasts Bone formation is affected, being particularly in evidence in the epiphyseal cartilage zone Proliferation of the cartilage cells is reduced and later arrested, and morphological changes take place in the cartilaginous plate which becomes the seat of numerous microscopic fractures and is reduced in its width. Adjoining the cartilage, in the interval between it and the bone, fibrous tissue and portions of the former trabeculae are found. Changes have been described in the muscles in severe examples of the disorder. No specific lesions are observed in the bone-marrow. The oral, dental and dermatological features are discussed elsewhere. Oedema and the accumulation of fluid within serous cavities may occur. When cardiac changes are demonstrable they

are usually referable to the left ventricle which is hypertroph[ied]. Haemopericardium and haemorrhages into other serous sacs m[ay] be noted. Within the gastro-intestinal system small ulcerated are[as] and haemorrhages in the gastric or intestinal wall may b[e] demonstrable.

Treatment of Vitamin-C-Deficient States

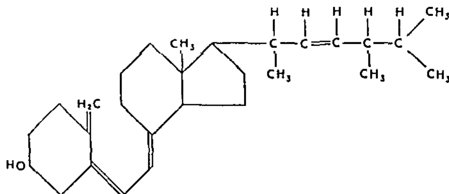
Vitamin C can be supplied from dietary sources, or as the crystalline product. The articles of diet rich in ascorbic acid have been indicated, and it is axiomatic that the faulty nature of the diet should be rectified to provide a sufficiency of all the essential nutrients. Oral administration of synthetic vitamin C will rapidly prove effective and the parenteral route is required only when local changes in the mouth prohibit oral medication or when there is an absorptive defect. The intramuscular route is preferable to the intravenous since by the latter process much of the vitamin is rapidly excreted in the urine. The dose of ascorbic acid required for saturation of the tissues varies considerably from case to case. For mild cases of vitamin-C deficiency, 100 mg. daily will prove adequate, but much larger quantities may be necessary in severe degrees of the malady. The urinary excretion of the vitamin following oral intake will provide an index of the amount which should be administered. Ralli and Sherry [345] observed that when small daily doses of the vitamin are given, the total quantity necessary to saturate the tissues is greater than if larger doses are prescribed. It is also necessary to ensure that, subsequent to the cure of the scorbutic condition, an adequate consumption of vitamin-C-containing foodstuffs is taken to prevent a future deficiency state.

VITAMIN D

THE TERM 'vitamin D' includes a group of compounds of similar chemical structure and possessing properties, common to all, which influence the metabolism of calcium and phosphorus in a characteristic manner. At least ten substances exhibiting vitamin-D activity are known to exist, although there are great differences in the degree of physiological activity of the individual members. They are derived from sterols and are composed of a complex aromatic hydrocarbon-phenanthrene-cyclopentane nucleus, with a side chain of variable structure. The sterols, of great importance in physiology and pharmacology, include cholesterol, corticosterone, oestrogens, progesterone, carcinogenic compounds and digitalis.

Chemical Properties – Only two of the various forms of vitamin D so far identified have sufficient potency to merit attention in clinical practice, vitamin D_2 and vitamin D_3. There is no vitamin D_1; the compound to which this designation was originally applied subsequently proved to be a mixture of calciferol and an inactive substance, lumisterol.

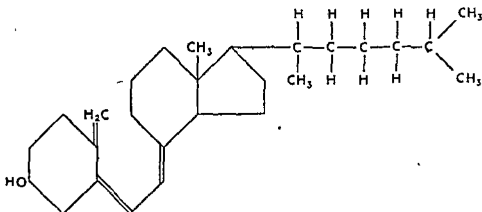
Vitamin D_2 is prepared by exposing ergosterol to the action of ultraviolet light; the effective rays in this process are those absorbed by ergosterol, that is, those with wave-lengths between 250 and 313 millimicrons; the maximum response occurs round about 280 millimicrons. In the irradiation of ergosterol, vitamin D_2 (calciferol) is not the only substance obtained and lumisterol, tachysterol, toxisterol and suprasterol are also evolved Over-irradiation yields a highly toxic product so that the irradiation of ergosterol in the preparation of calciferol must be arrested when the optimum amount of calciferol is formed, further exposure converting it into the toxic toxisterol Ergosterol does not show a wide distribution in nature and is found in appreciable quantities only in yeast and



ergot. It cannot be synthesized by animals nor can it be absorbed from ingested food. The pro-vitamin, ergosterol, is isomeric with calciferol. The photochemical change promoted by the ultraviolet rays results in molecular rearrangement.

Vitamin D_2, calciferol or viosterol (the last, a synonym introduced by the Council on Pharmacy and Chemistry of the American Medical Association), is very soluble in the common fat solvents but insoluble in water. It has been prepared in crystalline form. Calciferol, $C_{28}H_{43}OH$, has the structural formula (page 79):

The type of vitamin D present in the unsaponifiable fraction of fish liver oil was found to differ from calciferol and became known as vitamin D_3; some vitamin D_2, however, has also been isolated from fish-liver oil. Vitamin D_3 essentially is the naturally occurring form, although vitamin D_2 has been obtained from the cocoa bean and from certain fungi. Its precursor or pro-vitamin is 7-dehydrocholesterol, which on irradiation with ultraviolet rays is transformed to the vitamin. As with vitamin D_2, the ultraviolet rays of the sun and those from artificial sources, such as the carbon-arc lamp and the mercury quartz vapour lamp, are effective in converting the pro-vitamin into the active vitamin. Activated 7-dehydrocholesterol is produced when the skin, feathers and fur of animals is exposed to ultraviolet irradiation and, as in the case of ergosterol, the change is photochemical and other non-antirachitic substances are formed, although not of a toxic nature. Vitamin D_3 has been isolated in crystalline form. It may be obtained from concentrated fish oils and by the irradiation of pure 7-dehydrocholesterol. The structural formula of vitamin D_3, $C_{27}H_{43}OH$, is:–



Vitamins D_2 and D_3 show the same absorption spectra. Both are about equally effective in their antirachitic properties except in the chick, where vitamin D_3 is superior. An advantage of vitamin D_3 is that in its natural origin it is associated with vitamin A. The artificially prepared calciferol may not be entirely free from dangerous by-products.

Vitamin D_4 dihydrocalciferol is irradiated 22-dihydrocholesterol, but is of no clinical importance.

Units of Vitamin D. – The International Unit of Vitamin D is defined as the vitamin-D activity of 1 mg. of the international standard solution of irradiated ergosterol. One international unit equals 0·025 micrograms of calciferol The values of the international unit and of the United States Pharmacopoeia unit are identical, but the U.S.P. standard is a reference cod-liver oil that has been assayed against the international unit. The 'rat' unit and the 'chick' or A.O.A.C. (Association of Official Agricultural Chemists) unit are equal to the international unit.

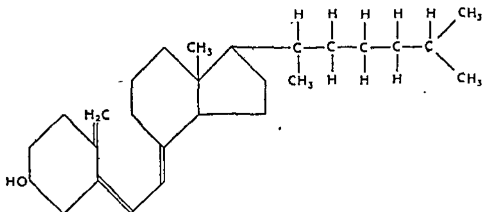
Physiology and Metabolism of Vitamin D. – Vitamin D is readily absorbed from the intestinal tract. The presence of bile salts, especially the salts of desoxycholic acid, is necessary for the absorption of the ingested vitamin. Mineral oils interfere with the process, while fats enhance the absorptive mechanisms. The main site of absorption is the small intestine and absorption is fairly complete in the human; in contrast a relatively large amount appears in the faeces of the chick and the cow While in fish the liver forms the special storehouse of the vitamin, a more generalized distribution is found in the tissues of man and significant amounts are present in the skin and brain and, to a lesser extent, in other organs with the exception of the liver which contains the largest quantities. A reserve store is thus built up in the body and can be drawn upon in times of deficiency Faulty absorption of vitamin D may attend intestinal diseases, particularly those associated with impaired absorption of fat, and the storage mechanism of the liver is disturbed in hepatic dysfunction Little if any vitamin D appears in the urine under normal conditions and although excretion occurs into the intestines the larger proportion of the vitamin is inactivated within the body Vitamin D can be absorbed from the skin and from intramuscular and intravenous injection. The quantity circulating in the blood has been estimated at between 50 and 135 I.U. per 100 c.c [346].

There still exists some disagreement on the precise action of vitamin D in calcium and phosphorus metabolism The skeleton is the sole store of calcium in the body containing about 97 per cent of the body's content and 75 per cent of its phosphorus. The calcium in the cortex of the bone is relatively constant but that present in the bony trabeculae is labile and is continually participating in the calcium exchanges in the body, whereby the serum calcium is maintained within a range of 9·9 to 11·1 mg. per cent in spite of variations in intake and excretion of the mineral [347]. Only some 25 per cent of the dietary calcium is available to the tissues, the remainder appearing in the faeces The degree of absorp-

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Physiology and Metabolism of Vitamin D.—Vitamin D is readily absorbed from the intestinal tract. The presence of bile salts, especially the salts of desoxycholic acid, is necessary for the absorption of the ingested vitamin. Mineral oils interfere with the process, while fats enhance the absorptive mechanisms. The main site of absorption is the small intestine and absorption is fairly complete in the human, in contrast a relatively large amount appears in the faeces of the chick and the cow. While in fish the liver forms the special storehouse of the vitamin, a more generalized distribution is found in the tissues of man and very small amounts are present in the skin and brain and, to a lesser extent, in other organs with the exception of the liver which contains the largest quantities. A reserve store is thus built up in the body and can be drawn upon in times of deficiency. Faulty absorption of vitamin D may attend intestinal diseases particularly those associated with impaired absorption of fat and the storage mechanism of the liver is disturbed in hepatic dysfunction. Little if any vitamin D appears in the urine under normal conditions and although excretion occurs into the intestines the larger proportion of the vitamin is inactivated within the body. Vitamin D can be absorbed from the skin and from intramuscular and intravenous injection. The quantity circulating in the blood has been estimated at between 50 and 135 I.U. per 100 c.c. [346].

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of preparations of the vitamin, or by heliotherapy, attention of course being directed also to the correction of the patient's diet. Cod-liver oil is a most convenient means of supplying vitamin D, and its nutritive properties and vitamin-A content are additional advantages. The taste of cod-liver oil has been advanced as an objection to its use, but generally there is no natural dislike actually present, the origin of the child's resentment to the oil being the parental attitude. A former criticism was the variable concentration of vitamin D present in different cod-liver oils, but this has been overcome by the establishment of a minimal standard of 85 I.U. per gram by the British and United States Pharmacopoeias. Only rarely is a true intolerance to the oil encountered, and this is usually accounted for by a state of fat intolerance. As a source of supply of an adequate intake of the vitamin, cod-liver oil is satisfactory, but in order rapidly to terminate a deficiency state, the concentrated preparations of vitamin D are preferable. Large doses of the vitamin can be administered in very small bulk. Numerous commercial preparations are available, the number of international units per volume being indicated. In the British Pharmacopoeia are calciferol (therapeutic dose 0·05 to 0·075 mg.), liquor calciferolis (therapeutic dose 0·6 to 1 mil.) and liquor vitamini D concentratus (dose 0·03 to 0·2 mil.). These suggested doses require further assessment in the individual case. The preparation of choice is the liquor vitamini D concentratus, 4 minims being equivalent to 2,000 units. The United States Pharmacopoeia issues an oleovitamina D synthetica which has a content of vitamin D of not less than 10,000 units per gram. Other preparations of vitamin D also exist, in association with vitamin A. Concentrates are also available for intramuscular administration. Halibut-liver oil is a richer source than cod-liver oil of both vitamins A and D.

The quantity of vitamin D in fish-liver oils varies with the species, the season of the year, the climatic conditions and the food supplies of the fish. In summer months the liver of the halibut shows a greater quantity of oil but the vitamin-D concentration is relatively low, whereas in winter months there occurs a reduction of the quantity of the oil, but an increase of the vitamin-D concentration. Much remains to be learned of the mode of origin of the vitamin D in the livers of fish.

Ultraviolet radiation of solar origin may be subjected to certain influences which vitiate its antirachitic function. The smoke-laden atmosphere of the large cities reduces its efficiency and the greater the distance it has to traverse the less valuable it becomes. Ordinary window glass absorbs the rays but the expense of the production of a type of glass which is without this undesirable quality is

state. The living plant contains practically no vitamin D. The liver of mammals shows comparatively small amounts and even these are very variable. Egg yolk contains the vitamin and may offer useful quantities although the content of the vitamin in hen's egg fluctuates greatly. Milk and butter are very poor in vitamin-D concentration but the lactalbumin of milk is considered to enhance the activity of the vitamin [353]. Fortified foods offer a means whereby the consumption of increased amounts of vitamin D may be attained. In Britain all margarine must contain 90 I.U. of vitamin D per ounce. The antirachitic properties of milk can be increased by irradiation or by the addition of a vitamin-D concentrate; when the former procedure is employed, it is essential that the process be carefully supervised for the vitamin-D content varies with the efficiency of the irradiation which, if maladjusted, may yield an inconstant and even unsatisfactory increase. The food consumed by the cow or the cow herself may be subjected to irradiation.

Sunlight and ultraviolet light activate the 7-dehydrocholesterol of the skin and afford an excellent source of antirachitic agents. This property resides in the radiations of less than 310 Angstrom units. Obviously much will depend on the amount of sunshine available and on the nature of the atmosphere. The action of the rays is directed upon the very superficial layers of the skin. From the irradiated skin the vitamin is absorbed into the blood stream. Animals and birds obtain considerable quantities from the dermal structures either by licking the fur or by the distribution of the secretion of the preen glands over the feathers, the irradiated secretion being subsequently removed on the beak.

Diagnosis of Vitamin-D Deficiency

Disturbances of the serum calcium and phosphorus levels may accompany the rachitic state. The alkaline phosphatase activity of the plasma is of great value in the diagnosis of early deficiency states and although an elevation is not specific to vitamin-D deficiency, the determination of the phosphatase value is the most satisfactory means of detecting persistence of the rachitic disorder. Radiological examination reveals characteristic changes which may demonstrate the presence of rickets before it can be ascertained by clinical methods. The manifestations and special methods of investigation of rickets are dealt with under that section.

Treatment of Vitamin-D Deficiency

Vitamin D may be supplied for therapeutic purposes in the form

of preparations of the vitamin, or by heliotherapy, attention of course being directed also to the correction of the patient's diet. Cod-liver oil is a most convenient means of supplying vitamin D, and its nutritive properties and vitamin-A content are additional advantages. The taste of cod-liver oil has been advanced as an objection to its use, but generally there is no natural dislike actually present, the origin of the child's resentment to the oil being the parental attitude. A former criticism was the variable concentration of vitamin D present in different cod-liver oils, but this has been overcome by the establishment of a minimal standard of 85 I.U. per gram by the British and United States Pharmacopoeias. Only rarely is a true intolerance to the oil encountered, and this is usually accounted for by a state of fat intolerance. As a source of supply of an adequate intake of the vitamin, cod-liver oil is satisfactory, but in order rapidly to terminate a deficiency state, the concentrated preparations of vitamin D are preferable. Large doses of the vitamin can be administered in very small bulk. Numerous commercial preparations are available, the number of international units per volume being indicated. In the British Pharmacopoeia are calciferol (therapeutic dose 0·05 to 0·075 mg.), liquor calciferolis (therapeutic dose 0·6 to 1 mil.) and liquor vitamini D concentratus (dose 0·03 to 0·2 mil.). These suggested doses require further assessment in the individual case. The preparation of choice is the liquor vitamini D concentratus, 4 minims being equivalent to 2,000 units. The United States Pharmacopoeia issues an oleovitamina D synthetica which has a content of vitamin D of not less than 10,000 units per gram. Other preparations of vitamin D also exist, in association with vitamin A. Concentrates are also available for intramuscular administration. Halibut-liver oil is a richer source than cod-liver oil of both vitamins A and D.

The quantity of vitamin D in fish-liver oils varies with the species, the season of the year, the climatic conditions and the food supplies of the fish. In summer months the liver of the halibut shows a greater quantity of oil but the vitamin-D concentration is relatively low, whereas in winter months there occurs a reduction of the quantity of the oil, but an increase of the vitamin-D concentration. Much remains to be learned of the mode of origin of the vitamin D in the livers of fish.

Ultraviolet radiation of solar origin may be subjected to certain influences which vitiate its antirachitic function. The smoke-laden atmosphere of the large cities reduces its efficiency and the greater the distance it has to traverse the less valuable it becomes. Ordinary window glass absorbs the rays but the expense of the production of a type of glass which is without this undesirable quality is

hardly warranted as a widespread procedure. Only in close proximity to the glass is a satisfactory amount of the rays obtained. Clothing prevents the access of ultraviolet rays to the skin. Exposure of a small area of the body surface will, however, suffice for the requirements of the human. In order to obtain greater benefit from the sun's rays, it is necessary to allow the child into open spaces free from obstruction of buildings. It is clear that in temperate climes sunshine as a therapeutic agent in rickets is but an ancillary measure, and is more important from a prophylactic aspect. It must be emphasized that the antirachitic response is not commensurate with the intensity of skin tanning and that excessive exposure may lead to untoward and dangerous effects, the degree of sensitivity being an individual matter. Other physiological effects of sunlight in man are reviewed by Blum [354].

Artificial sunlight can be obtained from the mercury quartz vapour or the carbon arc lamp. The duration of irradiation and the area of body surface exposed require careful grading. Particular caution must be exercised in fair-skinned subjects and the method is contra-indicated in febrile states, when heavy metals are being administered and in the presence of a photo-sensitizing disorder. Protection of the eyes with coloured glasses is necessary. As with the ultraviolet rays of sunlight, penetration of the rays may be prevented when the corneal layer is thick or dirty, although it has been already indicated that most of the conversion of 7-dehydrocholesterol takes place in the very superficial layers of the skin. It is not advisable to depend solely on sunlight for cure of a vitamin-D-deficiency state, if this be of any pronounced degree. The numerous claims advanced for a beneficial action of artificial ultraviolet irradiation in the promotion of health and reduction of infections are ill-founded. Controlled investigations such as that of Kennedy's [255] have revealed no advantageous action of ultraviolet radiation in these respects.

Hypervitaminosis D

Large amounts of vitamin D have been employed in the treatment of certain diseases This form of therapy is not without danger. In man the symptoms of hypervitaminosis are anorexia, nausea, vomiting, diarrhoea, sweating, frequency of micturition, muscular weakness, lassitude, headaches and depression. Freeman [356] found that patients with hypoparathyroidism might remain well for months on steady large dosage of vitamin D and a certain calcium intake, and then for no apparent reason they develop symptoms of toxicity. Debré *et al.* [357] emphasize the signs of involvement of the central nervous system, and state that the

clinical picture may resemble that of tuberculous meningitis. A fatal issue may ensue. In some instances the development of features of toxicity is preceded by a sense of well-being and by increased appetite.

Autopsy studies reveal calcification of the arteries and internal organs – kidneys, myocardium, stomach, bronchi, etc. The muscular coat of the larger-sized arteries is first involved in the vascular system and the calcification then spreads to the smaller vessels. Renal deposition of calcium principally takes place in the tubules and calculus formation may follow. Metastatic calcification may arise in any structure of the body. Divided opinion exists as to whether or not cellular damage precedes the calcification.

The importance of the recognition of early symptoms is obvious and gastro-intestinal or urinary disturbances in the course of treatment should be regarded as premonitory indications for an investigation for evidence of hypervitaminosis. Renal disease if associated with a decreased ability to excrete calcium will predispose to toxicity and in such conditions vitamin D should be administered with increased precautions. Nephritis and cardiovascular degeneration are contra-indications for massive vitamin-D therapy. A further influencing factor is the amount of calcium present in the diet and in this respect worthy of consideration is that ingested protein raises the amount of calcium absorbed from the bowel. McCance, Widdowson and Lehmann [358] consider that this offers an explanation for the claims of the anti-rachitic qualities of lean meat and dried milk. Reed *et al.* [359] observed that toxicity was more liable to occur when gastro-intestinal dysfunction, particularly diarrhoea and constipation, was present.

During treatment with massive doses of vitamin D, serum-calcium estimations should be carried out at weekly intervals and twice weekly or even more frequently in critical situations. The hyperphosphataemia produced is less marked and more irregular than the hypercalcaemia, and appears to be less dependent on the dietary phosphorus [360]. Harris and Innes [361] found the toxicity of irradiated ergosterol to be less on a low calcium diet. High calcium – low phosphorus diets increase the danger, small amounts of vitamin D produced a hypercalcaemia when given to rats subsisting on such a diet [362]. Hypercalcaemia calls for cessation or reduction of vitamin-D administration, but toxicity may occur in the presence of a normal serum calcium [363]. Albuminuria and urinary casts, particularly calcium casts, are other warning signals [364]. The exact dose which will prove toxic is difficult to estimate since there is much individual variation in sensitivity to vitamin D. Reed *et al.* [365] report toxicity following as little as 1,000 I.U. daily and in Bauer and Freyberg's [366]

See Addendum to this page at end of book

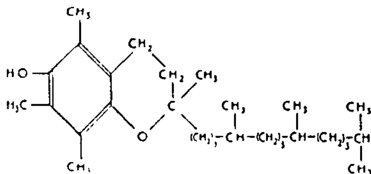
case 2,200 to 11,000 I.U. daily had similar ill-effects. On the other hand Snyder *et al.* [367] administering a daily dosage of 100,000–500,000 I.U. in 200 cases of chronic arthritis, observed no evidence of serious toxicity and radiological examinations revealed no areas of metastatic calcification. The important issues are that no patient should be treated with massive vitamin-D therapy unless under careful medical supervision, and that clinical symptoms are of primary importance in the early recognition of the disorder. A single massive dose appears usually to be safe and 1,000,000 I.U. have been presented without reaction [368].

Kombucha, a fungus used in the Far East to combat the process of ageing, was credited with a preventive action against toxicity of vitamin D, but this theory has been disproved [369]. Treatment of the disorder consists in the cessation of vitamin-D administration, the ingestion of large quantities of fluid and restriction of protein intake. Covey and Whitlock [370] advocate large doses of vitamin B. Thiamine and yeast are also valuable. Intravenous infusions of fluid may be necessary. As a rule, most of the changes of hypervitaminosis are reversible.

VITAMIN E

THE TERM 'vitamin E' refers not to a single substance but to a group of compounds whose physiological action is similar. Three members of the group have been isolated, alpha-, beta- and gamma-tocopherol, but other compounds possessing analogous activity exist in nature. Synonyms used for vitamin E include 'Factor X', 'anti-sterility factor', 'reproductive vitamin' and 'anti-encephalomalacia vitamin' The discovery of vitamin E was made almost simultaneously in three laboratories [371, 372, 373], and in 1936 Evans, Emerson and Emerson [374] isolated alpha- and beta-tocopherol from wheat germ oil and gamma-tocopherol from cotton-seed oil

Chemical Properties – Alpha-tocopherol (tokos, childbirth; phero, to bear), $C_{29}H_{50}O_2$, is isomeric with beta- and gamma-tocopherol, the last two showing only two methyl groups in the aromatic nucleus Vitamin E shows the following chemical formula: –



The three tocopherols have been synthesized Beta- and gamma-tocopherol have less biological activity than alpha-tocopherol, which itself is less potent than the natural product. The tocopherols are unsaturated alcohols and are soluble in fats and fat solvents but *are only sparingly soluble in water They are classified with the* fat-soluble vitamins, but in the animal body are associated chiefly with protein and in plants with the cytoplasm rather than with the oil deposits Vitamin E behaves in its primary function as an essential component of tissue, as a water-soluble vitamin which requires a lipide carrier for its transport, and only in its secondary function, as an anti-oxidant, does it conduct itself as a truly fat-soluble vitamin [375] In its natural state vitamin E is very stable but, while it is unaffected by visible light, ultraviolet rays, in which a characteristic absorption spectrum is obtained, inactivate it to

some extent; heat in the absence of oxygen, strong acids and alkalis exerts little deleterious effect. The tocopherols are oils and form esters; pure tocopherols are readily susceptible to oxidation but the esters are comparatively stable. Rancid fats have a markedly destructive action on vitamin E. Alpha-tocopheryl acetate possesses equal biological potency with alpha-tocopherol and has the great advantage of increased stability.

Sources. – Little vitamin E is present in the animal organism and in its natural occurrence the vitamin exists predominantly in plant materials. Here it is found as a complex mixture, different sources containing different proportions of the tocopherols. Vegetable oils offer the best source. Wheat-germ oil is particularly rich in its content of vitamin E, but it is also contained in considerable quantity in cotton-seed oil, lettuce oil, rice-germ oil and other seed-germ oils. Olive oil is devoid of the vitamin and only very small quantities can be recovered from arachis oil. Fish-liver oils are also poor in vitamin-E content. In the plant kingdom a large group of compounds exist ('inhibitols') which oppose the oxidation of vegetable fats; while the tocopherols are members of this group they are, in nature, associated with other substances of even greater anti-oxidant capacity and by their action the vitamin E is preserved in a reduced state. Information regarding the mode of synthesis of vitamin E in plants is still lacking. The seeds contain a greater concentration than the leaves and the plant embryo more than the seed. There is no evidence that synthesis of vitamin E occurs in the animal organism.

Unit and Determination of Vitamin-E Content. – Synthetic racemic alpha-tocopheryl acetate has been adopted as the international standard of vitamin E. An international unit is the specific activity of 1 mg. of the standard preparation, being the average amount which, when given orally, is capable of preventing resorption-gestation in rats deprived of vitamin E.

Although vitamin E exhibits a characteristic absorption spectrum (maximum at 290–294 millimicrons) this only affords a measure of estimating the pure or almost pure substance, since in its naturally occurring form it is associated with other compounds which produce absorption in a similar range and so interfere with the estimation. Various chemical methods are available. Two employ the oxidation of vitamin E, by ferric chloride or gold chloride, and one the production of a red colour following the heating of the vitamin with alcoholic nitric acid. In the first two instances other substances may interfere by their capacity to reduce the chemicals and must be removed for accurate determination; in the third procedure inactive oxidation products of vitamin E also yield a red coloration.

The biological methods give sufficiently accurate results but only if controls are employed concurrently. Prevention or cure of resorption-gestation in rats, gain of weight of rats during pregnancy, prevention of muscular dystrophy in animals, and the fertility test on *Daphnia magna* are among those which have been described.

Function of Vitamin E and Deficiency States in Animals. – The primary function of vitamin E in man is unknown, nor has it been conclusively demonstrated that a deficiency state can arise in the human. The importance of the vitamin in human nutrition in association with its anti-oxidant action is appreciated, however. Vitamin A and carotene are protected against oxidative destruction by the tocopherols and members of the vitamin-B complex appear to be similarly influenced.

Deficiency of vitamin E in the diet of animals results in syndromes which show marked variation in different species. These syndromes are referable to the muscular system, the central nervous system, the reproductive system and growth Many of the experimental diets utilized to induce these conditions contained considerable amounts of cod-liver oil or other fish oils; their action was due to the presence of unsaturated fatty acids which promote oxidative destruction of vitamin E either in the diet or digestive tract [376]. Lesions of the voluntary muscles were found in the offspring of mother rats partially deprived of vitamin E, by Olcott [377], no changes being demonstrable in the central nervous system. Evans and Burr [378] had noted the abrupt onset of paralysis in such animals, protection from which was afforded by the administration of wheat-germ oil to the young Goettsch and Pappenheimer [379] described a similar affection in rabbits and guinea-pigs and proposed the term, 'nutritional muscular dystrophy' Sheep, goats, ducks, mice and hamsters are other animals in which the condition can be produced Vitamin E exerts a curative effect. Pathological examination revealed loss of striation of the muscle fibres, multiplication of the sarcolemma nuclei which were irregularly placed and [illegible]
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could occur throughout a muscle or only in patches and active reparative changes could proceed simultaneously Certain chemical alterations were revealed on study of the dystrophic muscle. The potassium and magnesium are decreased and the sodium increased in the muscle [380] and there is a diminution in total creatine content [381] although the relative concentration of creatine in esterified form is said to be much greater than normal [382]. A rise in the excretion of creatine in the urine precedes any clinical evidence of the dystrophy [383]. Only when the muscle showed

advanced dystrophic changes was a disturbance of total phosphorus content of the muscle noted by Goettsch *et al.* [384], and then an increase was observed in association with calcification of the fibres, while a decreased concentration was found in those muscles which did not show calcification. Hypercholesteraemia was striking in rabbits suffering from nutritional muscular dystrophy and the cholesterol content of the muscles was increased [385]. The oxygen consumption of dystrophic musculature increases markedly while the administration of vitamin E leads to pronounced reduction, but no similar effect was witnessed in the normal muscle [386]. Houchin and Mattill [387] demonstrated that alpha-tocopheryl phosphate, which is water-soluble, when added to the Ringer-Locke perfusion fluid, brings about a reduction in the oxygen consumption of dystrophic rabbit and hamster muscle.

Involvement of the involuntary musculature is striking in the turkey in which the gizzard musculature undergoes ischaemic necrosis with secondary fibrotic changes [388]. In other animals, apart from the uterine muscle, the smooth muscle is but little affected. A yellowish-brown coloration of the uterus appears [389] but there is no associated alteration of response to pharmacological substances such as acetylcholine and adrenaline [390].

Einarsen and Ringsted [391] published an important work on the lesions in the central nervous system in the vitamin-E-deficient adult rat. Essentially the pathology showed close approximation to a combination of tabes dorsalis and progressive muscular atrophy; in a few the pyramidal tracts were diseased and the lesions resembled those of amyotrophic lateral sclerosis, and the muscular changes were interpreted as secondary to the neurological lesions. Monnier [392] could discover no pyramidal affection in an analogous investigation and the skeletal muscles demonstrated considerable lesions such as segmental necrosis. Gutierrez-Mahoney *et al.* [393] reported a pathological picture of much greater severity than that encountered by Einarsen and Ringsted. Wolf and Pappenheimer in their experiments on rats, found no abnormalities in the central nervous system [394]. It has been suggested by Pappenheimer [395] that the diversity of the recorded findings in the nervous system may be attributable to variations in technique and that in view of the contradictions, the therapeutic use of vitamin E in amyotrophic lateral sclerosis and other degenerative diseases of the spinal cord rests upon a very insecure experimental basis. Contradictory reports have been presented on the involvement of the motor end-plates of the muscles [396, 397, 398].

Vitamin-E deficiency in chicks results in nutritional encephalomalacia [399]; tremors, inco-ordination, and involuntary movements terminated in death. Widespread involvement of the central

nervous system occurred but the site of the maximum onslaught was the cerebellum and the changes there were considered to be the result of vascular occlusion The ganglion cells and neuroglia are destroyed and haemorrhage and capillary thrombosis are evident. Should the chick survive, evidence of reparative processes is observed [400] Rat embryos of vitamin-E-deficient mothers were found by Mason [401] frequently to show cutaneous and intra-cerebral haemorrhage, a further manifestation of the possibility of vascular changes attending a vitamin-E-deficiency state. Dam and Glavind [402] described the 'alimentary exudative diathesis', another form of vitamin-E deficiency in chicks; generalized oedema appears and with it effusions into the serous cavities, oedematous changes in the brain and lungs and congestion of intestines. The two vitamin-E-deficiency syndromes of the chick are respectively produced by variations of the experimental diets [403]

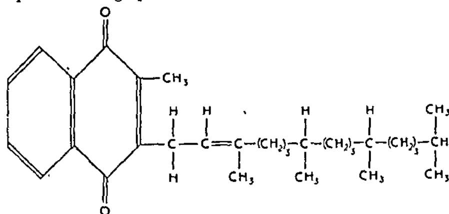
The function of vitamin E in reproduction in animals has been studied chiefly in the rat. Male rats, maintained on a diet deficient in vitamin E from early life, are sterile; shortly after the onset of sexual maturity degenerative changes develop in the seminiferous epithelium and within a few weeks the seminiferous tubules are almost entirely devoid of germ cells [404]. Should the hypo-vitaminosis be of mild degree only, the spermatozoa suffer loss of motility and show degenerative changes. The degenerative lesions in the germinal epithelium appear first in the mature cells. In the established deficiency state pronounced alterations are evident, a peculiar finding being the fusion of many cells to form a syncytial mass containing many nuclei; after several weeks almost no germ cells may be evident in the seminiferous tubules. Male mice reared for 400 days on a similar regime [405] or maintained through several generations on vitamin-E-deficient diets [406] exhibited no testicular injury Female rats reared on a diet lacking in vitamin E demonstrate, in normal fashion, oestrus, ovulation, conception and implantation of the developing foetus. 'Resorption sterility' occurs, however, the embryo and foetal membranes showing abnormalities of growth which are succeeded by intra-uterine death and resorption of the foetus [407]. Mason [408] attributes these events to abnormalities of the vascular system, and concludes that in this specific nutritional deficiency a structural weakness of the vascular system ensues, leading to stasis and ischaemia of the foetal tissues In spite of repeated resorptions, the sexual functions remain unaffected and pregnancy may be completed in normal manner if sufficient vitamin E is administered [409].

Reproduction is not improved beyond normal levels when large quantities of the vitamin are supplied, nor is the development of the ovaries and uterus, opening of the vagina or cornification of

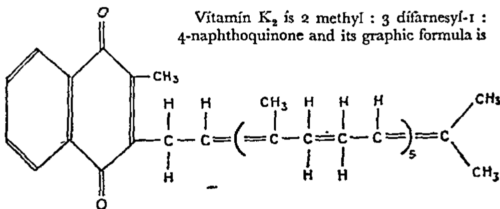
VITAMIN K

VITAMIN K was so named by Dam whose researches revealed the occurrence of a haemorrhagic disease in chicks raised on a synthetic diet in which the essential substance lacking was the 'Koagulationsvitamin' [425, 426]. It was found that alfalfa was a rich source of the substance and that putrefied fish meal also supplied large quantities; the factor derived from the former source received the designation of vitamin K_1 and from the latter source the term vitamin K_2. A pigment, phthiocol, present in the acetone fraction of the tubercle bacillus, possesses a degree of anti-haemorrhagic activity and has been referred to as vitamin K_3.

Chemical Properties of Vitamin K. – Vitamins K_1 and K_2 are fat soluble but insoluble in water. They are thermostable while exposure of the pure substances to sunlight or artificial light induces loss of potency. A destructive effect is exerted by alkalis and strong acids. Oxidative processes destroy the vitamins. Typical absorption characteristics are displayed by vitamin K in the ultraviolet range. Vitamin K_1 is 2-methyl-3-phytyl-1 : 4-naphthoquinone. The graphic formula is



Vitamin K_2 is 2 methyl : 3 difarnesyl-1 : 4-naphthoquinone and its graphic formula is



Vitamin K_3 which is water soluble, is 2-methyl-3-hydroxy-1 : 4-naphthoquinone.

It is now appreciated that the activity of the vitamins K depends on the 1, 4 naphthoquinone group. Following the demonstration of the quinone structure, naphthoquinones were synthesized in the laboratory and their anti-haemorrhagic properties investigated. Many have been prepared and of particular importance is 2-methyl-1 : 4-naphthoquinone which is also known as vitamin K_4 menaphthone (B.P.C.) and in America as menadione. This compound possesses a higher degree of activity than the naturally occurring vitamins K. Vitamin K_4 is fat soluble and is administered in oil by the intramuscular route. It is also prepared in tablet form or in oil solution for oral use; by combining menaphthone with sodium bisulphite or sodium sulphate a water-soluble preparation is obtained which is suitable for intravenous administration. Vitamin K_5, 2-methyl-4-aminonaphthol hydrochloride is water soluble.

Metabolism of Vitamin K. – The vitamin-K content of the intestine is derived from ingested foodstuffs and from bacterial synthesis. For the absorption of the natural compounds bile salts are necessary. The water-soluble synthetic analogues do not require the presence of bile in the intestinal tract, nor is it necessary to administer bile-salts with the fat-soluble synthetic oral compounds when no biliary obstruction exists. Ingested mineral oils seriously interfere with the absorptive process, as do intestinal lesions. The exact site of absorption has not been definitely established, but it is considered to be the upper part of the small intestine [427]. Only very small amounts circulate in the blood and man has no great capacity to store the vitamin in the tissues, the liver contains certain quantities but no great concentration of vitamin K. Fatal hypoprothrombinaemia may occur within a week. Excretion in the urine does not appear to take place, but large amounts are recoverable from the faeces, representing that portion which has not been absorbed and particularly the fraction derived from intestinal bio-synthesis.

Function of Vitamin K. – Vitamin K functions in the body in the formation of prothrombin and is essential for normal coagulation of the blood. Prothrombin is a glycoprotein. Quick [428, 429] considered that prothrombin was a complex of calcium and two components, prothrombin A, which disappears from oxalated stored blood, and prothrombin B which disappears from dicoumarol blood and probably from the blood of vitamin-K-deficient subjects. The prothrombin level is restored by mixing the two types of blood. Stored blood and plasma should be effective in controlling the hypoprothrombinaemia produced by dicoumarol. Quick [430]

found to possess 1 unit of prothrombin per c.c. supplies the figure of the number of prothrombin units of the blood. One unit of thrombin is that quantity which under standard conditions will produce clotting of 1 c.c. of a fibrinogen solution in fifteen seconds, and 1 unit of prothrombin is the quantity of prothrombin required to form 1 unit of thrombin; 1 unit of prothrombin is equal to 1 unit of thrombin. In the first stage of the test the prothrombin was converted to thrombin and in the second stage the amount of thrombin formed was measured. For clinical purposes it has been found that this method is too complicated and it has been largely replaced by the one-stage tests.

(2) *The One-Stage Methods.* – Two methods are available; in one plasma is used and, in the other, blood.

(*a*) *Plasma Prothrombin Time:* In this examination the clotting time of oxalated plasma at 37·5° C. is determined. A fixed amount of calcium is added and an excess of thromboplastin, and the time required to produce clotting is measured. This time includes that necessary for the transformation of prothrombin to thrombin, and for the interaction of the latter with the fibrinogen. Several modifications of the type of thromboplastin used have been proposed. Quick employed cephalin procured from rabbit brain [439]. Among other thromboplastins are preparations from dried brain, lung extracts, Russell-viper venom, and lecithin *plus* Russell-viper venom. The normal prothrombin times vary with the different methods employed. A disadvantage of tissue thromboplastin preparations is the tendency for their potency to wane with keeping. Other different procedures which have been suggested consist of alteration of the anticoagulant, e.g. heparin, and variation in the quantity of calcium used.

With levels of plasma prothrombin even as low as 60 per cent of normal, performance of the test on undiluted plasma may fail to reveal any deviation from normal. To overcome this difficulty prothrombin times are carried out not only on the whole plasma, but also on serial dilutions of the plasma; a 12·5 per cent dilute plasma is often used.

(*b*) *The 'Bedside' Test:* Ziffren and his colleagues [440] devised a method which consists of adding 0·9 c.c. of freshly drawn off blood to 0·1 c.c. of a standard thromboplastin. The tube is regularly tilted until clotting is observed. The clotting time is compared with that of a normal individual and expressed as a percentage.

Various micro-methods are reported and involve similar principles to the tests described. They are useful in children in whom venepuncture may be a difficult procedure.

Prothrombin times are valuable in the determination of vitamin-K deficiencies, as a guide to therapy, in the diagnosis of liver disease and in controlling dicoumarol therapy. Aggeler *et al.* [441] emphasize that the use of one random subject as a normal standard may lead to considerable error and at least five normal individuals should be tested with the same specimen of thromboplastin. The prothrombin time of peripheral arterial blood is generally somewhat in excess of that of venous blood, but the difference is insignificant, and either may be used [442]. The test should be conducted as soon as possible after withdrawing the blood, since the clotting time has been shown to increase in proportion to the time of storage [443]. Electrolyte concentration, pH and temperature should be kept as constant as possible since each may influence the result.

Vitamin-K Deficiency in Animals – Examination of vitamin-K deficiency in the chick was responsible for much of the knowledge originally gained of the effects of lack of this essential substance. The deficient chick develops subcutaneous, intramuscular and internal haemorrhages. Minor abrasions were associated with prolonged bleeding and with delayed clotting time and low blood prothrombin level. Bleeding did not ensue until the prothrombin level had fallen to 10 to 15 per cent of normal. An important factor influencing the development of the deficiency syndrome was the diet of the hen, when the diet was rich in vitamin K the chicks were found to be more resistant to the production of the disorder than were the controls. The transmission of the vitamin apparently takes place through the yolk since yolk supplements were protective, whereas egg albumin was not [444]. In the production of experimental vitamin-K deficiency not only is it necessary that the basal diet be free of the vitamin, but also that bacterial growth in the foodstuffs be prevented. Fish meal or rice bran if moistened before incorporation in the diet will prevent the incidence of the disease. From putrefying fish meal, which is known to be a rich source of vitamin K_2, a strain of organisms was isolated; large quantities of the vitamin appeared when these organisms were grown on cultures [445]. Brinkhaus [446] points out that since the faeces of chicks manifesting the haemorrhagic features of the vitamin deficiency contain vitamin K, it is probable that the vitamin is evolved in the lower part of the intestine, too low to allow of absorption. Prothrombin deficiency has also been produced in rats, mice, pigeons, etc., but many attempts to effect such changes in mammals by feeding diets lacking in vitamin K have been unsuccessful, probably owing to ability to absorb sufficient of the vitamin synthesized in the intestines.

Causes of Vitamin-K Deficiency and Hypoprothrombinaemia in Man

(1) *Nutritional Inadequacy of Vitamin K.* – Although reports exist of vitamin-K deficiency resulting from inadequate consumption of vitamin-K-containing foodstuffs, this is a very uncommon event. Kark and Lozner [447] recorded the examples of 4 patients, who had been living on a diet practically devoid of fruit and green vegetables, with prolongation of the plasma prothrombin times; other pathological states were present and may have participated by producing impairment of intestinal absorption, but this could not have been of serious degree, since all responded with an elevation of the plasma prothrombin levels on the day following vitamin-K administration by mouth. Eighteen cases of nutritional vitamin-K deficiency in man were reported by Scarborough [448].

(2) *Lesions of the Alimentary Tract.* – The naturally occurring vitamin K, being fat soluble, will suffer defective absorption in any state which interferes with fat absorption. Hence a deficiency may appear in the steatorrhoeas. Ileostomy, diarrhoeal states, intestinal obstruction and short-circuiting operations may also operate in a similar manner. The adverse action of mineral oils has already been mentioned. The question of possible interference with, or failure in, the intestinal synthesis remains to be elucidated. Liver disease and biliary fistula in vitamin-K nutrition are considered elsewhere.

(3) *Drug Interference.* – Cattle fed on spoiled sweet clover hay develop a haemorrhagic disease which is attributable to a fall in the circulating prothrombin. It has been discovered that the substance active in its causation is dicoumarin (dicoumarol), 3,3, methylene-bis-(4-hydroxycoumarin), $C_{19}H_{12}O_6$. The structures of vitamin K and dicoumarin are similar. When administered by the oral route dicoumarin reduces the coagulability of the blood within twenty-four to forty-eight hours and its effect does not disappear until three to seven days following cessation of its intake, and may still be demonstrable several weeks later if considerable amounts have been supplied. In addition to promoting an increase in the plasma prothrombin time, dicoumarin impairs clot retraction, decreases the adhesiveness of platelets, and accelerates the sedimentation of erythrocytes, but does not effect the clotting power of the blood or plasma *in vitro*. Dicoumarin exerts its action on the liver so that formation of prothrombin B does not take place. No other action has been discovered on the hepatic tissues and no evidence of impairment of liver function was discovered in animals receiving large doses of the compound Dicoumarin has been employed clinically chiefly

for the prevention and treatment of [illegible]. This form of therapy is not without danger and haemorrhagic phenomena may appear. Daily prothrombin estimations should be conducted. The drug should be used with caution in the presence of an ulcerative or granulating lesion, following recent surgical operations, and in debilitated or cachectic individuals. Certain conditions contra-indicate its use: renal insufficiency, haemorrhagic disorders, severe heart disease, hepatic disease, subacute bacterial endocarditis, [illegible], vitamin-K deficiency and towards the end of pregnancy and in the first few days of the puerperium. With regard to the last two mentioned states, it has been observed in the lactating rat that, when fed dicoumarin, haemorrhages may appear in the sucklings. When dicoumarin therapy is indicated in the puerperal period, it would be advisable to remove the baby from the breast while the effects of dicoumarol persist. For the treatment of haemorrhage secondary to dicoumarin, transfusion of fresh blood, repeated if necessary, may be indicated. In most instances large doses of vitamin K by the intravenous route are effective [449]. On the other hand failures by the latter method have been reported, as by [illegible] [450] and by Davidson and McDonald [451]. The latter authors subsequently reported that large doses of vitamin K_1 oxide were effective in reversing the hypoprothrombinaemia [452]. Vitamin K does not produce an immediate rise in the blood prothrombin, this occurs in two hours with a maximum effect in eight hours. When the quicker action of whole blood is not required vitamin K may be used alone [453].

Sulphonamide drugs may depress the activities of the vitamin-K-synthesizing organisms of the intestine and lead to diminution of prothrombin levels. Salicylates are important agents in the production of hypoprothrombinaemia and are considered elsewhere. Park and Engelberg [454] showed that quinine sulphate induces a lowered plasma prothrombin level which could be counteracted by vitamin-K administration and they advised caution in the use of quinine in the presence of any haemorrhagic features of malaria. Quinidine would appear to exert a similar action, but digitalis has not been found to influence the prothrombin levels in the blood either in the recovered state of cardiac failure, or when congestive phenomena are pronounced [455]. Cotlove and Vorzimer discovered no alteration in the prothrombin concentration of the blood when intravascular thrombosis complicated the cardiac derangement, this finding contrasts with the heightened plasma prothrombin levels encountered in thrombophlebitis complicating post-operative recovery [456].

(4) *Idiopathic Hypoprothrombinaemia* – Several examples of this

abnormality have been reported. Rhoads and Fitz-Hugh [457] record the case of a young male, previously diagnosed as haemophilia, who suffered from repeated haemorrhages, from one of which he succumbed. The plasma fibrinogen was qualitatively defective. Post-mortem examination revealed some atrophy of the liver columns of too slight a degree to be considered as the cause of the defect. A similar case was encountered by Murphy and Clark [458] who postulated the possibility of a specific inability of the liver to synthesize prothrombin even in the presence of liver function normal in other respects. Both sets of investigators failed to obtain any beneficial response from vitamin-K administration. The patient of Austin and Quastler [459] suffering from idiopathic hypoprothrombinaemia was observed to show a normal bleeding time, increased coagulation time, poor clot retraction, normal platelets and a negative tourniquet test; there was no evidence of an anti-Rh agglutinin. Liver function tests were negative and autopsy did not reveal significant liver damage. Unresponsiveness to vitamin K and a tendency to familial incidence appear to be of common occurrence in the disorder. In the example cited by Quick [460] the low fixed prothrombin level apparently originated from birth and was present in other members of the family. It was concluded that the defect was on the maternal side and inherited [illegible]

while the acquired form is caused by toxic or neoplastic interference with fibrinogen formation [461].

Other conditions associated with hypoprothrombinaemia are discussed under the appropriate sections.

Treatment of Vitamin-K Deficiency

In the British Pharmacopoeia there is menaphthonum (menaphthone, menadione) and in the United States Pharmacopoeia, menadioni sodii bisulphis and injectio menadioni sodii bisulphitis. Vitamin K will exert no haemostatic effect in patients showing normal prothrombin times. When an absorptive defect is present, very large oral doses of vitamin K may prove effective, but a much more certain response is obtained by parenteral administration. In liver disorders vitamin K may not act if the fault lies in the inability of the liver to utilize the vitamin in the formation of prothrombin; in obstructive jaundice and biliary fistula the water-soluble form, given orally, will raise the lowered plasma prothrombin level, provided hepatic damage is not of great severity. Blood transfusion increases the plasma prothrombin content although rarely

beyond 10 to 15 per cent of the former value; as a temporary expedient it may be life-saving, but vitamin K should be given at the same time, preferably, in such emergency, by the intravenous route. When the treatment of a disease calls for the use of drugs known to exert hypoprothrombinaemic effects it is wise simultaneously to administer vitamin K as a prophylactic measure. Very large doses are indicated in conditions of overdosage of dicoumarol. It is not enough to control haemorrhagic manifestations and at all times the vitamin should be prescribed until normal plasma prothrombin levels are reached and maintained. The synthetic analogues are now employed. The customary dose of menadione is 2 mg. orally or parenterally, but much larger doses can safely be given as the indications arise. Estimations of the prothrombin level are the guide to dosage. When operative procedures are contemplated vitamin K should be prescribed if the plasma prothrombin level be below 70 per cent and a period of treatment should be adopted sufficient to elevate the level to normal if conditions permit, and if the hypoprothrombinaemia be responsive to vitamin-K therapy. Following the operation the treatment should be continued in accordance with the circumstances of the individual case. Of particular importance in this respect is surgical intervention in disease of the hepatic and biliary systems.

Since cod-liver oil inunction is succeeded by a prompt rise in the plasma-vitamin-A content, Page and Bercovitz [462] applied methyl naphthoquinone in an ointment form base to the skin of 9 patients. In 5 a dermatitis developed. This would not seem a desirable procedure.

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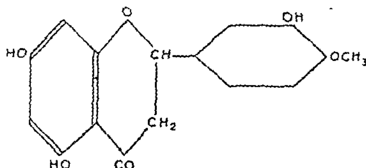
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VITAMIN P – THE ESSENTIAL FATTY ACIDS

VITAMIN P

SZENT-GYÖRGYI and his co-workers [463] in 1936 applied the term 'vitamin P' to a substance which they isolated from paprika and lemon juice and which they claimed was of greater efficacy in the treatment of increased capilliary permeability than vitamin C. The designation 'vitamin P' was used because of its association with paprika and permeability. The active fraction obtained from lemon juice was named 'citrine'.

Properties of Vitamin P.—Vitamin P is composed of two flavanone glucosides, hesperedin and eriodictin. These compounds are closely related, eriodictin being demethylated hesperedin. It has been suggested that eriodictin is the chalone of hesperedin. There is still considerable doubt as to the exact nature of vitamin P since concentrates of the vitamin have been shown to exert a markedly greater activity than crystalline hesperedin [464]. Hesperedin shows the following structural formula:–



Vitamin-P activity has been demonstrated particularly in fruits and green leaves. Lemon peel and orange peel show a significant concentration. Bacharach and Coates have analysed the vitamin-P content of fruits and vegetables [464].

Extracts have been prepared from various plants and have been found to exhibit activity in restoring capillary fragility to normal. These extracts are of similar chemical structure, and especially important is rutin which has been derived from high-grade, cured tobacco, buckwheat, forsythia, elder flowers and violets. Rutin has been successfully employed in the treatment of states of increased capillary fragility but its exact relationship to vitamin P has not yet been elucidated.

Vitamin-P activity can be estimated by biological methods. Bacharach, Coates and Middleton [465] employed a suction cup which was applied to the shaven skin of a guinea-pig. The critical petechial pressure was regarded as that necessary to produce

haemorrhage in the part. The vitamin-P activity of the substance in question was graded against a standard reference substance and was expressed in provisional units Crystalline hesperedin possessed an activity of 100 provisional units (P.U.) per gram. Chemical methods have proved unsatisfactory. A red colour is produced from citrin by the action of magnesium and concentrated hydrochloric acid. This reaction does not appear to be specific to vitamin P and the red colour resulting from heating citrin with sodium hydroxide has the same disadvantage.

Oral or parenteral administration of the vitamin is effective. Its excretion has been demonstrated in the urine. The tissues contain but small concentrations of vitamin P.

Studies of Vitamin P in Animals and in the Human Subject. – Guinea-pigs, rendered scorbutic by experimental diets, show an increased capillary fragility which is improved following the administration of vitamin C, but which is restored to normal only after the addition of vitamin P. Claims are also advanced that a similar state exists in scorbutic human subjects since vitamin C alone did not significantly alter the capillary fragility [466]. Vitamin P is not a substitute for vitamin C, and it is suggested that a deficiency of the former results in petechial haemorrhages rather than in the grosser forms of bleeding found in ascorbic acid-deficiency conditions. Scarborough [467] also points out that vitamin P has no effect on other important manifestations of scurvy such as tissue hydration, gingival haemorrhages, anaemia, knee flexion and the general clinical condition.

The clinical evidence of the value of vitamin P is conflicting. Considerable confusion exists with regard to the capillary fragility because different standards for its estimation have been adopted and because many factors affect its level. Age influences the capillary resistance which shows its highest level during the first few weeks of life and which gradually diminishes during infancy until the adult level is reached; marked fluctuations are found in the individual level of the capillary resistance and in the level at various parts of the body, the values increasing from a minimum at the head to a maximum at the extremities [468]. These and other considerations make it difficult to assess the efficacy of vitamin P.

Scarborough states that vitamin P produces an increased capillary resistance in the scorbutic subject either before or after treatment with vitamin C and that in such subjects ascorbic acid or vitamins A, B_1 and D are without effect in this direction. He considers that vitamin-P deficiency in man is manifested by pains in the legs on exertion, pain across the shoulders, weakness, lassitude and fatigue; an invariable feature is an altered capillary fragility and perhaps also petechial haemorrhages in the skin

which are to be found particularly in areas exposed to pressure. Scarborough [469] describes the features which ensued from an experimentally induced vitamin-P deficiency state in 2 human subjects. The capillary resistance was reduced, the bleeding time was slightly prolonged and petechial haemorrhages were evident in the skin.

Vitamin P has been used in the treatment of purpuric and allergic conditions. Jersild [470] described a case of Schonlein-Henoch purpura which promptly responded to vitamin-P therapy but which had proved resistant to vitamin-C administration. He put forward the view that this disorder was attributable to deficiency of vitamin P. Kugelmass [468] reports 5 cases of purpura of different aetiologies which were relieved by vitamin P. An example of thrombocytopenic purpura developing after an attack of measles is recorded by Miller [471]; a vitamin-P preparation was effective in producing a cessation of the haemorrhagic features and in restoring the capillary fragility to a normal level. Favourable responses to vitamin P have been reported in the decreased capillary resistance which occurs during the treatment of syphilis with arsenical and bismuth preparations [472] and in haematuria [473]. According to Raunert haemorrhage from the urinary tract originating from conditions such as nephritis and neoplasm could be arrested by vitamin-P administration. Rapaport and Klein [474] observed an abnormal capillary fragility in 49 of a series of 100 allergic children. Twelve were selected who had shown persistently abnormal capillary fragility responses and vitamin P was given in doses of 100 mg. daily by mouth for a period of six months; in 10 the capillary fragility reverted to normal under this medication but in the other 2 the dose had to be increased to 150 mg. daily before a normal level was attained. Negative results following vitamin-P therapy in states of reduced capillary fragility and in purpura have been recorded by several observers [475, 476], and Beaumont and Dodds [477] conclude that vitamin P does not appear to be efficacious in the treatment of purpura rheumatica or of mechanical purpura.

No haematological changes are associated with vitamin-P deficiency and administration of the vitamin does not increase the capillary resistance of normal subjects. The dose of vitamin P prescribed in treatment is empirical and is influenced by the purity of the preparations. The crystalline glycosides are usually administered in daily doses of 50 to 150 mg.

THE ESSENTIAL FATTY ACIDS

The term 'essential unsaturated fatty acids' was introduced in 1930

by the Burrs [478]. Vitamin F and vitamin F_1 are other designations. It is not universally accepted that the essential fatty acids should be classified as vitamins. Linoleic acid, linolenic acid, arachidonic acid and linoleyl alcohol are active in the treatment of the fat-deficiency syndrome of animals but only linoleic and arachidonic acid are considered essential, for either alone can relieve the deficiency state. Burr [479] states that, since linoleic acid is of plant origin and arachidonic acid derived from animal sources, the essential nutrient is linoleic acid.

Linoleic acid ($C_{18}H_{32}O_2$) is found in vegetable and seed fats such as corn oil and cotton-seed oil. Linolenic acid ($C_{18}H_{30}O_2$) has a similar distribution but arachidonic acid ($C_{20}H_{32}O_2$) is almost completely absent from the plant kingdom and is present in animal tissues. Fish oils, including cod-liver oil, are poor sources of the essential unsaturated fatty acids and in the manufacture of margarine these are converted into a saturated state. Little is known of the mode of origin of linoleic and linolenic acid in plants but it would appear that the animal body is capable of converting these substances into arachidonic acid. All three compounds are colourless and readily dissolve in organic solvents and alkaline solutions although they remain insoluble in water. The state of unsaturation of the essential fatty acids allows them to unite with iodine which is consequently decolorized and the quantity of iodine so affected affords a measure of the degree of unsaturation; the 'iodine number' is employed to indicate the latter property and denotes the number of grams of iodine which are decolorized by 100 grams of fat. Oxidative procedures effect changes in the unsaturated fatty acids with the production of rancidity, a change which is associated with deleterious action on other essential dietary factors, particularly vitamins A and E. Considerable uncertainty still exists as to the mode of physiological function of the essential fatty acids in the body.

In 1929 Burr and Burr [480] described a syndrome in young rats which appeared when these animals were maintained on a diet of very low fat content and which was curable by the administration of certain unsaturated fatty acids. The rats developed scaliness of the skin, caudal necrosis, marked retardation of growth and renal lesions, and death occurred after a short period. Male rats showed loss of sexual desire and became sterile, while in the female ovulation often became greatly deranged, or ceased altogether, and if pregnancy ensued resorption of the foetus might follow or a poor litter be produced. Lactation was noted often to fail. A peculiar feature of the syndrome was a high water consumption without any associated increase in the urinary output. The first signs to appear in the deficiency state were the

dryness and scaliness of the skin, initially confined to the paws and later extending over the whole body. The hair became thin particularly in the region of the face and eyes. An important finding was the suppression of the dermatological manifestations when conditions of high humidity prevailed. Although a gain of weight was observed in the early stages, loss of flesh was striking as the disorder progressed. The basal metabolic rate and the respiratory quotient were usually elevated. Investigation of the syndrome has been largely confined to the rat. The goat, cow, chicken and pig have been maintained for short periods on low-fat diets without obvious evidence of untoward effects [481]. In mice a scaly dermatitis and early death resulted and in dogs, dryness and scaling of the skin and dryness of the hair [482].

For rats 20 to 25 mg. of linoleic acid daily has proved sufficient to maintain satisfactory growth and reproduction, and in curative experiments daily doses of 50 to 100 mg. have been effective [483]. The normal rat requires 1 per cent of its diet to be constituted of linoleic acid and it has been conjectured that a similar proportion of the dietary intake of essential fatty acids denotes the requirements of man. While there remains no absolute justification for an assumption that in the human body deficiency of the essential fatty acids will produce similar lesions to those of the experimental animal, an association between the health of the skin and the essential fatty acids does not appear improbable. The clinical observations on this aspect are dealt with elsewhere. Hansen and Burr [483] indicate that a deficiency state in the young rat is obtained only after a diet practically free of fat has been consumed over relatively long periods of time. The possibility of infants subsisting for prolonged periods on diets practically devoid of fat yet adequate in other respects is very remote, so that a dietary origin of a fatty acid-deficiency syndrome in the human is highly improbable. Nevertheless, the essential fatty acids may prove a useful adjunct in the treatment of certain skin diseases [483].

Since information on the metabolism of fatty acids in the tissues and on the possibility of their destruction within the body is scanty, little can be concluded as to other methods of producing a deficiency state of the essential fatty acids in man. Prolonged intestinal malabsorption of fat in the human offers the most closely analogous state to that of experimental conditions in animals. Idiopathic steatorrhoeas represent prolonged deficiency of fat, and Hansen and Burr [483] review the association of dermatological defects with those disorders. Bennett *et al.* [484] record 7 examples of this association and further examples are reported by Konstam and Gordon [485] and by Riley [486]. The investigations of Luzzati and Hansen [487] are of much interest. They found skin lesions in

3 out of 10 cases of coeliac disease. Estimation of the iodine number of the fatty acids in the serum in coeliac disease produced very low figures as compared with those of normal controls. While the amount of fatty acids in all the fractions of the blood lipides was normal, the degree of unsaturation was abnormally low in all fractions. No irrefutable evidence is as yet forthcoming as to the ability of the animal body to synthesize the essential fatty acids but McHenry and Cornett [488] consider that this remains a distinct possibility providing that the necessary dietary constituents are supplied.

A content of liver and kidney is not disturbed by cooking, nor is the vitamin D of beef dripping.

The vitamins A and D of fatty fish are but little influenced by storing and cooking. There is no vitamin C contained in fish as consumed. Boiling inactivates the small amount of thiamine present in fish by about 20 per cent and about 50 per cent disappears during grilling and baking. Reference has already been made to the adverse effects of repeatedly used frying fat.

Potatoes are so prominent in the ordinary diet that consideration of their vitamin-C content becomes a matter of importance. Loss of ascorbic acid in potatoes is least with steaming: then in ascending order come boiling, baking and pressure cooking. Stewing may reduce the ascorbic acid values to zero. The best method of conserving the vitamin C of potatoes is to cook them in their skins. Mashing is especially detrimental.

The acidity of fruits protects them from the destructive action of stewing on their vitamin-B_1 and vitamin-C contents; these vitamins diffuse out into the juices which should be consumed. Addition of sodium bicarbonate before stewing is often utilized to reduce the acidity of the fruit and so the amount of sugar necessary. Since alkalis destroy ascorbic acid, their use should not be encouraged, except in allowing half a level teaspoonful per pound of fruit. Cooking salt on the other hand exerts a protective influence against the oxidation of ascorbic acid. With regard to manufactured fruit drinks, these contain only a small amount of ascorbic acid unless otherwise stated on the label. Drinks freshly prepared from the fruit offer satisfactory quantities of vitamin C.

Canning. – As with all methods for the preservation of food, canning employs a state of conditions unfavourable to the existence of spoilage organisms. The prepared food, in its sealed container, is exposed to a sufficient degree of heat to destroy these spoilage organisms. The site of most of the canning factories is in proximity to the areas in which the foodstuffs are produced, so that the problem of vitamin loss during storage hardly arises. Erroneous conceptions as to the effect of canning on the vitamin content of the food are still prevalent. Experiments have shown that animals over several generations have thrived better when fed on canned foods. The best advantage of canned foods can be obtained only if the can liquid, be this brine, water or syrup, is utilized. The concentration of the water-soluble vitamins in the can liquid may exceed that present in the solids.

Vitamin A and carotene, being insoluble in water and heat resistant in the absence of oxygen, are practically unaffected by the canning processes.

The loss of potency of the thiamine content will be considerable

only if in the processing the heating periods are prolonged at temperatures of over 100° C. and if the medium be alkaline. In alkaline reaction the decline of thiamine may be as much as 80 per cent, whereas in acid solution the destructive effect of heat processing is slight. Acid-canned foods, e.g. fruits, require relatively light heat treatment in contrast to the non-acid canned foods. The information available on riboflavin and nicotinic acid is scant but canned foods may contain 80–90 per cent of the original value of each. The content of thiamine, riboflavin and nicotinic acid in canned meat is small. In the preparation of corn beef the meat is cut and exposed to boiling water for fifteen minutes; the B vitamins tend to be washed out in the process.

Contact with the copper of the tin was at one time the cause of a serious diminution in the ascorbic acid content of the canned foodstuff, but this source of loss has now been avoided by appropriate lining of the container. Fruits and vegetables in the canned state are very good sources of vitamin C Several factors are responsible for this conservation of the vitamin-C value. Storage is reduced to a minimum and the field crops are harvested at the most desirable stage of maturity, only the best quality materials being incorporated. The oxidative enzymes are destroyed and the air is removed from the food and the tin in the process of canning, thus protecting the vitamin C against destructive oxidation. The preparation of some vegetables, for example peas and spinach, requires a blanching procedure whereas such substances as tomatoes and citrus fruits are not subjected to this operation. Blanching may be accompanied by some loss of ascorbic acid, but this attains no serious dimensions

Vitamin D and other vitamins would not appear to suffer significant reduction as a consequence of canning, and canned herrings, sardines, salmon and mackerel are among the few good sources of dietary vitamin D.

Fermentation. – Fermentation does not appear to exert any specific influence on the vitamin content of the fermented product which, however, remains as susceptible to the destructive agencies as the original material.

Abt and Farmer [508] encountered anorexia, increased peristalsis, dermographia and erythema, and considered that these features may be attributable to sensitivity to ascorbic acid. Wilson and Lubschez [509] observed similar symptoms in young children receiving massive doses of vitamin C. An interesting finding was a depression in the concentration of the vitamin in the white cell layer of the blood of children which followed intakes of 9 mg. per kg. or more, as compared with intakes of 1·5 to 2·9 mg. per kg. of body-weight. They raise the possibility of a lowered renal threshold for the vitamin succeeding prolonged therapy, and advise against the administration of vitamin C over a long period of time to children whose previous intake has been adequate.

Vitamin C has a diuretic action. Animal experiments had demonstrated this effect and Abbasy [510] found that a test dose of 700 mg. of vitamin C resulted in a rise in the volume of urine voided. Shaffer [511] points out that the onset of the diuretic action corresponds with the occurrence of tissue saturation. If a normal reserve is present, this usually occurs on the third day. Parenteral injection produces a more rapid saturation of the body, but is not attended with any appreciable diuresis. Ten patients with cardiac decompensation showed a small diuresis when ascorbic acid was given by mouth. When given by the intravenous route, no appreciable diuresis resulted. In combination with mercupurin oral ascorbic acid administration produced a urinary output of from one-half to two and a half times greater than with the mercurial diuretic alone. The diuresis is believed to be due to altered colloid osmotic pressure and not to the production of an acidosis.

References to the toxic and pharmacological actions of the other vitamins are made elsewhere in the text.

BIOSYNTHESIS OF VITAMINS

The animal body is able to synthesize certain vitamins although the capacity to do so varies with the species. Synthesis may take place in the tissues or through the agency of micro-organisms in the alimentary canal. Ruminants, for example, can exist on diets deficient in vitamin B with no apparent adverse effects, and an exogenous source of vitamin C is not necessary for many animals.

During the first six weeks of life, synthesis of vitamins in the intestines does not occur in the dog, rat and ruminant and only becomes evident once the proportions and relationships of the intestinal flora are established. Sulphaguanidine and succinylsulphathiazole administration interferes with and may totally arrest the vitamin-producing functions of the intestinal organisms.

Sulphonamide therapy may precipitate a deficiency state, as for example the haemorrhages of vitamin-K deficiency. Administration of these sulphonamide preparations to individuals with low vitamin reserves requires careful supervision with regard to the possibility of precipitation of an overt deficiency state.

Among the vitamins which have been shown to be synthesized in the gut of various animals are thiamine, riboflavin, nicotinic acid, pyridoxine, biotin, folic acid, pantothenic acid, inositol and vitamin K. The production of vitamins seems necessary for the growth and multiplication of the intestinal bacteria which normally do not enter into competition with the body for the vitamins supplied in the diet. The mere presence of vitamins in the faeces cannot be accepted as a measure of the amount available to man. Part of the faecal vitamin content is contained within the bacteria themselves and as such is unavailable to the tissues until death of the bacterium liberates its vitamin content; however, growth of the bacteria in artificial media has revealed the major portion of the vitamins to exist in free state in the medium.

The opposite effect of biosynthesis – destruction of vitamins in the bowel – has also received attention. Destruction of vitamin C can be brought about by the action of a large variety of intestinal organisms. Young and Rettger [512] and Benesch [513] concluded that in the human caecum there is normally an equilibrium between those organisms which destroy and those which produce nicotinic acid. Williamson and Parson [514] suggested a destructive action on vitamin B_1 in the human intestines Viewed in the light of these possibilities, the faecal vitamin content would represent the difference between the amounts synthesized and ingested and which had escaped absorption, and the amount destroyed in the gut.

A problem which still awaits solution is the extent to which man can depend for his nutrition on the bacterial sources of vitamin supply Najjar and Holt [515] fed nine adolescent men on a diet deficient in thiamine; five developed vitamin-B_1 deficiency and showed practically no thiamine in the faeces, while there was an appreciable amount in the stools of the others. This amount however reached zero levels following administration of succinylsulphathiazole. The authors considered that absorption of vitamin B_1 normally takes place from the large intestine since a retention enema containing the vitamin resulted in an increased urinary excretion of thiamine. Alexander and Landwehr [516] criticized the conclusion of Najjar and Holt that the vitamin B_1 of intestinal organismal origin is available to man since it is largely contained within the bacterial body and since most of the vitamin is present in the form of cocarboxylase which cannot be absorbed until dephosphorylated

by enzymes which are absent from the large intestine. The interpretation of the results of the retention enema they consider to be untenable as evidence of a physiological process because of the very large amounts of thiamine employed. Emerson and Obermeyer [517] noted that thiamine-depleted rats, in whose diet corn starch served as the carbohydrate, excrete appreciable quantities of vitamin B_1 in their stools. That the total thiamine was not nutritionally available, they state, was shown by the subsequent development of polyneuritis and death of the animals; the faecal thiamine of the deficient rats was not available for nutritional purposes when administered curatively by the oral route. Ellinger and Coulson [518] stated that the excretion of nicotinic acid in man may be greater than the intake, and that the quantity arising from bacterial synthesis may amount to as much as 80 per cent of the daily consumption. According to Najjar *et al.* [519] the sum of the urinary and faecal excretions of riboflavin may exceed the intake; twelve human subjects showed a daily faecal excretion which varied between 200 and 600 micrograms on a dietary consumption equivalent to 60 to 90 micrograms daily. Similarly bacterial synthesis of vitamin K in man is well established.

Several problems await further elucidation. The degree of availability of the vitamins synthesized in the gut for human nutrition remains *sub judice*. If under ordinary circumstances the human body utilizes this source, then our conception of man's vitamin requirements requires modification. The conditions which may diminish this supply are important and include local states of the intestine and the relative proportions of the various types of intestinal organisms. Dysfunction of the gastro-intestinal tract may produce conditioned deficiency states by interference with biosynthesis as well as by excessive loss via the faeces, defects of absorption and diminished intake due to derangement of the appetite. Deficiency disease in some instances may be an expression of an imbalance between synthesis and destruction of vitamins in the intestines. The occasional resistance of deficiency syndromes to oral vitamin therapy may possibly be explained by increased destruction in the bowel. An excellent review of the subject is provided by Najjar and Barrett [520].

BERIBERI

THE ORIGIN of the term 'beriberi' is obscure. It is considered to have been applied as a description of the abnormal gait which was held to simulate that of sheep. The name 'kakke' was derived from the Japanese, meaning heaviness and weakness of the lower limbs. Accounts of the disease date back for many centuries.

Aetiology. – Beriberi is a nutritional deficiency disorder, and is associated with the consumption of a diet consisting largely of over-milled rice and refined cereals. Rice as it is harvested has tough, fibrous coverings, which, since they are indigestible, are removed by various means in order to render the foodstuff suitable for consumption. This removal of the outer integuments is associated with considerable loss of essential nutrients, including vitamin B_1. The polyneuritis produced by Eijkman in fowls fed on polished rice, was curable by extracts of the rice polishings, and the condition was considered to be analogous to human beriberi. The present-day view is that beriberi is not a manifestation of a thiamine deficiency alone, but that lack of other vitamins enters into its causation. Rice polishings contain members of the vitamin-B complex, in addition to vitamins A, D, and E, and while vitamin-B_1 therapy will dramatically relieve many of the symptoms of beriberi, some manifestations of the disease prove resistant to thiamine alone, but are improved following the administration of vitamin-B complex.

The deficiency theory of beriberi is not universally accepted, and toxins have been incriminated in the aetiology. Polished rice is thought to be attacked by organisms, and the toxins ingested as a consequence precipitate the malady. Some samples of sound rice are also considered to contain toxic products. An endogenous source of poisonous substances, originating from the gastro-intestinal tract, has in addition been postulated, and certain investigators hold that the vitamin-B_1 deficiency allows the endogenous or rice toxins to operate, the therapeutic action of thiamine being explained by its neutralizing action on the toxins. Infantile beriberi is discussed in a subsequent section.

Beriberi occurs principally in the Far East, where rice occupies a predominant position in the dietary. India, Japan, China, East Indies, and the Malay States show a very high incidence of the disease. White bread forms a large part of the food intake in Newfoundland and Labrador, and accounts for the frequency of beriberi in these parts. Outbreaks have been reported on board ship, in besieged cities, and in mental institutions and prisons.

Clinical Features. – As the disease affects adults, various types of clinical syndromes can be segregated. Acute or fulminating beriberi implies a condition in which severe cardiac manifestations are the outstanding presentations of the disorder and are of sudden onset and rapid development. Chronic beriberi is usually considered under divisions of the dry and wet forms; the distinction made is that, in the former, peripheral neuropathy is the outstanding feature, whereas in the latter, oedema and collections of fluid in the serous sacs constitute the predominant findings. The signs and symptoms of beriberi are so varied that these different types cannot be sharply demarcated, and all gradations and combinations are encountered. For practical purposes, however, it is useful to consider beriberi in relation to this form of classification.

Acute Beriberi

This variety is rarely encountered in the Western hemisphere. It is of relatively infrequent occurrence as compared with the chronic forms, upon which it may be superimposed. In the latter event sudden cardiac failure ensues after gastro-intestinal, neuritic or cardiac disturbances have existed for weeks or months. When acute beriberi appears as the primary manifestation, the onset is abrupt. Gastro-intestinal upset, severe abdominal and praecordial pain are complained of, and rapid dilatation of the heart develops. Palpitations and breathlessness are pronounced, the pulse rate is very rapid, the veins in the neck are engorged, and congestive features become evident. With the development of the last-mentioned characteristic, pulmonary oedema, enlargement of the liver and oedema of the dependent parts are noted. Arterial pulsation may be marked, and a 'pistol shot' murmur may be audible on auscultation over the artery, attributable to the increase in pulse pressure. Cardiac murmurs and a tic-tac rhythm are frequently present, and electrocardiographic changes, the most prominent of which are alterations in the *T* wave, shortening of the *P-R* interval and increase in the duration of the Q-R interval, are demonstrable. Sudden death may follow any, even minor, degree of exertion. Cases are also reported of abrupt cessation of the cardiac action in the absence of any preliminary signs of heart failure or of beriberi.

There is some divergence of opinion regarding the precise nature of the agencies responsible for the acute or pernicious form of beriberi. Some contend that a toxic factor is the major operating influence, rather than the thiamine deprivation itself. Others postulate a lesion of the vagus nerve. It has been suggested that the toxin is free to exert its deleterious effects in the absence of the antagonistic action of thiamine.

Dry Beriberi

Dry beriberi develops in a very gradual manner, and the early stages may persist for long periods before the overt clinical picture appears. A partial deficiency explains the larval varieties which, if not corrected, will progress to the paralytic stage. At first the complaints are those of indefinite ill-health and fatigability. The *lower limbs feel heavy and tire more readily after exertion.* Tingling sensations, numbness and other paraesthesias are complained of, and the muscles of the legs become tender to touch. At this stage physical examination may reveal some objective sensory loss in the distal parts of the feet and diminution or even loss of the ankle-jerks. With advancement of the disease, the sensory symptoms become more pronounced and more uncomfortable, burning sensations and muscular cramps being prominent. Sensory loss follows a peculiar distribution. It is first demonstrable over the outer side of the leg, thence spreading to the dorsum of the foot and medial aspect of the leg. The sole of the foot is much less involved than the dorsal surface. Below the umbilicus an area of hypoaesthesia may be evident, and there are also descriptions of diminished sensibility around the lips. The amount of exertion necessary to promote fatigue of the lower extremities steadily decreases. The weakness of these limbs advances until actual paralysis ensues and muscular wasting appears and progresses. Weakness of the dorsiflexors of the foot is an early feature of the motor affection and eventually proceeds to complete foot drop. Impairment of sensation by now will have become more widespread, and, as with the motor weakness, is most evident in the distal portions of the limbs The hyperaesthesia of deep pressure contrasts with the loss of the other modalities, but deep sensation is nearly always preserved. Drop-foot results in a 'steppage gait'. True ataxia attributable to defect of the proprioceptive fibres is rare. Examination reveals loss of the knee and ankle jerks and the reaction of degeneration on the electrical testing of the muscles. It is to be appreciated that the rate of development will vary widely, that all degrees of the affection may exist, and that in some patients the disease may not progress beyond a certain level, and in others may spontaneously resolve.

Involvement of the arms may be found in severe beriberi. While this usually succeeds the changes in the legs, the upper extremities may demonstrate the earliest features of the disorder, and this particularly in subjects whose work necessitates a much greater [illegible]

neck usually escape. Control of the sphincters is retained until the very late stages, although weakness of the abdominal musculature may interfere with defaecation. Attention has recently been directed to lesions of the cranial nerves in beriberi, in view of the neurological conditions which have developed in prisoners of war in World War II. Aphonia and alteration of voice have been described under three different categories. A very dilated auricle may compress the left recurrent laryngeal nerve, the vocal cords may become oedematous, or neuritic changes may be demonstrable in the recurrent laryngeal nerves. It is in infantile beriberi that aphonia is a relatively frequent event. Bilateral facial weakness and palsy and degenerative changes in other cranial nerves have been reported. Special importance is now attached to the incidence of retrobulbar neuritis in beriberi, and this aspect is reviewed by Denny-Brown [521]. Apparently the association has been mentioned not infrequently by the Japanese school, whereas the connexion is either denied or considered a rarity by writers of other countries. Denny-Brown analysed the reports of Kagawa [522], who concluded that a close relationship existed between beriberi and retrobulbar neuritis. Denny-Brown found that the evidence presented was open to a different interpretation, namely that the retrobulbar neuritis was caused by a deficiency disorder distinct from beriberi; a similar interpretation is also applied by Denny-Brown to the occurrence of deafness, described as a manifestation of beriberi. Mental symptoms are absent or not prominent in beriberi. Defects of memory may occur. In the course of recovery, Denny-Brown observed that absence of the ankle-jerks and great muscular tenderness persisted long after resolution of the sensory changes and muscular weakness; weakness of dorsiflexion of the ankle and of the big toe also showed a slow rate of recovery.

Wet Beriberi

The outstanding feature of the wet form of beriberi is oedema, which first makes its appearance in the lower limbs. The scrotum and lumbar region are next affected, and the face may share in the swelling. Accumulation of fluid in the serous sacs leads to ascites, hydrothorax and hydropericardium. In the earliest stages oedema becomes manifest in the legs only after exertion. Gravity influences the distribution of the oedema, which is of a firmer nature than that which attends heart or kidney disease. Bizarre distributions of the excessive tissue fluid have also been described. The factors involved in the genesis of the tissue retention of fluid are not considered to be attributable to cardiac or renal failure, but to disorder of the small blood vessels. Hypoproteinaemia may

complicate beriberi, but in the average case it plays little part in the causation of the oedema. The occurrence of cardiac failure will superimpose an oedematous process different in origin from that of ordinary beriberi, and the lack of movement of paralysed limbs with retarded venous return may also participate.

Wet beriberi frequently co-exists with neuritic manifestations which, however, in large part may remain concealed by the oedema. Cardiac enlargement, when present, usually implicates the right side, the left becoming affected at a subsequent stage. Tachycardia, lability of the pulse rate, a bounding quality of the pulse, increased pulse pressure due to fall of the diastolic level and 'pistol-shot' and cardiac murmurs are among the signs encountered when the heart is involved. When congestive failure appears, liver enlargement and tenderness are demonstrable, and the neck veins are engorged. The circulation rate is normal or increased. Further features are discussed in the Section on Vitamins and Disorders of the Heart.

Other Manifestations

Gastro-intestinal symptoms are frequent. Loss of appetite, nausea, vomiting, and abdominal pain and diarrhoea may occur. Anaemia and signs referable to a deficiency state of other vitamins have been not infrequently observed. Corneal vascularization, dermatitis, oral lesions and signs of ascorbic acid inadequacy may be mentioned. Malaria, dysentery and intestinal infestations are among the common complicating disorders which, by their very presence, are predisposing factors and further increase the severity of the nutritional deficiency.

Pathology

The post-mortem findings of the acute cases are largely concentrated in the heart In such instances there is little or no evidence of wasting, and the changes in the nervous system are relatively slight. The heart is hypertrophied and dilated, the right side showing the more pronounced degree. The wall of the right auricle may be so reduced in thickness as to be paper-thin, and the cavity may dilate to enormous dimensions. Another structure demonstrating marked dilatation is the conus arteriosus. Small haemorrhages may be visible below the pericardium or in the myocardial musculature. Pulmonary oedema and chronic venous congestion of the liver, spleen, kidneys and intestines may be discerned. Anasarca, hydrothorax and hydropericardium are common. Hydropic degeneration of the myocardium and oedema of the interstitial spaces may be demonstrable microscopically and, in the less acute cases, fatty degenerative changes. The explanation of the

mechanism of the cardiac alterations is not quite clea nerve affection would not account for the predominant sided lesion. The presence of a generalized capillary and a dilatation will result in an increased return of blood to side of the heart, which hypertrophies under the increased and later undergoes dilatation; the vasodilatation, it is su arises from the accumulation of intermediate prod carbohydrate metabolism [523].

Degenerative lesions of the peripheral nerves show a variation in degree; the changes range from very slight to involvement of the myelin sheath and axis cylinder. The is most pronounced in the distal portions of the nerve. Th of the lower limbs show the most severe alterations, since usually first involved, but changes may be revealed in a pheral nerve, spinal or cranial. The involuntary nervous shares in the pathology, and lesions are demonstrable in the and other plexuses and their branches. The myelin is bro into irregular portions and may eventually disappear. Fra tion and atrophy of the axis cylinders occur, their stage of a ment depending on the duration and severity of the disease

The cells of the posterior root ganglia demonstrate de tive changes. There is little to be made out as a rule macroscopic examination of the central nervous system, ar morphological abnormalities detectable on microscopic ins are expressions of ascending degeneration of the affected p nerve roots and disturbances in the trophic cells. Thus, may be discerned in the posterior columns, anterior horn c the medullary nuclei. Cases have been described which n a diffuse oedema of the central nervous system.

The involved skeletal musculature may show atrophy, swelling, fatty degeneration, and loss of cross striation findings are secondary to the lesions of the nerves, and are the picture of all types of polyneuritis.

Treatment

Unless the disorder be mild, the patient should be confined A satisfactory balanced diet is instituted, and this sho supplemented with yeast, rice polishings, wheat germ and The carbohydrate content of the diet should be kept at low [illegible] stages and foods rich in thiamine, such a [illegible] be poorly tol [illegible] e the quantit sumed, or to allow only small amounts to be eaten at fr intervals.

Thiamine is supplied in dosage appropriate to the severity of the condition. Parenteral administration is employed in the proper circumstances, and intravenous injection is particularly indicated in the acute cardiac type; this route is not without possible danger. Usually 30–50 mg. of vitamin B_1 daily suffices, and probably nothing is to be gained by larger dosage if intestinal absorption be not defective. Treatment must be continued over long periods, and it is advisable to prescribe a maintenance dose in the recovered case. Other vitamins should also be administered simultaneously, since beriberi is probably a polyvitamin deficiency state and since vitamin imbalance is thus avoided.

When there is cardiac involvement exertion should be restricted until the condition is controlled. Digitalis therapy may prove beneficial, but the mercurial diuretics are not usually necessary. Removal of pleural fluid may be indicated to relieve dyspnoea and pressure symptoms. Care of the paralysed limbs is carried out in the usual manner, but massage may greatly provoke the muscular pain and should be delayed until the latter has eased. Contractures and pressure sores must be avoided. Symptomatic treatment is conducted as the occasion arises, and specific therapy is necessary in the presence of a complicating disease.

While the acute cases usually respond in a dramatic manner, enormous quantities of the oedematous fluid being rapidly removed in the urine, the chronic cases show a slow rate of progress and complete recovery may never ensue The residual manifestations are those attributable to irreversible damage of the nervous system, or to resistance to the present mode of therapy.

PELLAGRA

PELLAGRA WAS described in Spain in the seventeenth century but the first adequate study was recorded by Gasper Casal in 1735. Casal, who was physician to King Philip V, applied the term 'mal de la rosa', and considered that the malady was due to some toxic or infectious factor in corn. The name 'pellagra' is derived from pelle agra, meaning rough skin, and was introduced in 1771 by the Italian physician, Frapolli. Subsequently the disease became recognized in other parts of the world, although it was not until 1907 that its prevalence in the southern regions of the United States was appreciated and reported by Searcy [524]: about that time pellagra assumed almost epidemic proportions in these areas.

Aetiology. – Pellagra is a disorder chiefly found among maize-eaters and until 1914 the prevailing view attributed its causation to a hypothetical toxin present in the maize. In 1914 Funk [525] suggested a dietary deficiency as the aetiology and this hypothesis was upheld by the feeding experiments of Goldberger and his colleagues [526, 527, 528] in human volunteers. The present-day opinion as to the nature of pellagra is that it is a dietary-deficiency disease which may arise from inadequate ingestion of the appropriate foodstuffs, or from defective absorption or increased requirements of the essential factors. Goldberger considered that a single nutrient, vitamin B_2, was the curative measure, but it is now established that vitamin B_2 is a complex substance, containing nicotinic acid, riboflavin, pyridoxin and other ingredients. Nicotinic acid alone will not cure all the manifestations of pellagra; with this form of therapy the dermatological, gastro-intestinal and mental disturbances and the stomatitis are relieved. Spies and his co-workers [529] hold that there are three well-defined syndromes distinguishable in the clinical picture. The first is attributable to nicotinic-acid deficiency and accounts for the skin, oral, alimentary and mind derangements and for the vulval and perineal affections; a deficiency of riboflavin is responsible for the red, shiny lips, the excoriations at the angles of the mouth, eyes and nostrils and the seborrhoeic, scaling skin changes found about the naso-labial folds, bridge of the nose and forehead; lastly the neuritic manifestations are accredited to lack of vitamin B_1. In addition to the deficiency of the B vitamins it is obvious that the dietary inadequacy of pellagrins will give rise to insufficiency of other essential nutrients and in this respect a depletion of the vitamin-C reserves, for example, may exist as an associated but not aetiological condition.

That pellagra could not be transmitted to normal man by

administration of the blood, secretions or extracts from the pellagrous lesions, afforded proof against the infectious theory. Nevertheless there are certain facts which indicate the possibility of a toxic substance in maize as a contributory cause. Damage to maize during storage is particularly liable to promote the incidence of pellagra. In America, during the prohibition era, pellagra was encountered in places, formerly free of the disorder, among individuals who had consumed crude alcohol distilled from maize.

Chick [530] advanced the theory that a combined intoxication and vitamin deficiency existed, a toxic substance developing in maize or in some other cereal. The possibility that corn meal itself may participate in the evolution of pellagra was indicated in experiments conducted on dogs maintained on corn meal-containing Goldberger diets. Dehydration, lack of thirst and haemoconcentration, characteristic of human pellagra and black tongue, were produced by the corn meal diets but not by simple nicotinic-acid deficiency [531]. On a dry weight basis, corn contains as much nicotinic acid as eggs, milk, polished rice, oats and rye and often more [532]. Krehl *et al.* [533] studied the effect of corn grits on the nicotinic-acid requirements of dogs and found that their administration greatly increased the nicotinic-acid requirements of growing dogs, whereas other foods such as milk and casein, which are even poorer in nicotinic-acid content, tended to reduce this requirement. Corn grits may operate by disturbing the absorption of nicotinic acid or by interfering with intestinal synthesis of the vitamin. These authors consider that on a heavy grit diet the nicotinic-acid requirements of man are increased threefold and suggest that the enrichment of corn meal and other milled corn products should be increased beyond present standards considered adequate. Since milk and milk products are held to encourage intestinal synthesis of nicotinic acid, their inclusion in increased amount in the diet affords an alternative measure for preventing the adverse action of corn meal. This beneficial action is believed to be produced by the tryptophane present in the foodstuffs. Cystine also exerts a beneficial effect in nicotinic-acid nutrition. The position requires further clarification but it would appear that the multi-deficiency origin of pellagra may be occasioned by lack of supply of the essential nutrients and by substances present in certain foodstuffs which affect their vitamin content or the intestinal synthesis of these nutrients. Proteins rich in the essential amino-acids will check the development of the disease, while the toxic products of spoiled maize and other cereals encourage its occurrence.

Pellagra is common in those countries which are adjacent to the Mediterranean and Black Seas. The incidence is particularly

high in Egypt and in the southern regions of the United States. While in Roumania pellagra has shown an increase, the disease has markedly declined in frequency in Italy. Spain, Portugal, South America, China and Japan are among other countries where pellagra is a not uncommon disorder. In Britain pellagra is rarely encountered and is then usually determined by organic disease, particularly gastro-intestinal abnormalities, or it appears in institutions in slow development among the aged and infirm and the mentally deranged.

Secondary pellagra implies the development of the disorder in spite of the intake of a diet satisfactory for ordinary requirements. Morphological and functional changes, pregnancy and lactation are among the causal agents. A clear-cut distinction of the secondary form is not always possible since the anorexia and nausea which may accompany the original disease may lead to a reduction in food intake to subnormal levels. The subject is reviewed by Bean, Spies and Blackenhorn [534] who record 338 cases.

Diseases of the jaw, adentia and dysphagia may be complicated by pellagra due to the consumption of an ill-balanced diet of liquid or pultaceous consistency. The malady may appear in patients suffering from chronic gastritis, peptic ulcer or gastric carcinoma. In the intestines hypermotility may interfere with digestion and absorption, and pathological changes in the mucosa greatly impair the absorptive mechanism. Synthesis of the vitamin by the intestinal flora may be affected and the destruction of the vitamins increased. The alimentary disorder of pellagra becomes superimposed and a vicious cycle is established. Ulcerative colitis, neoplastic disease, chronic diarrhoea, tuberculous enteritis, chronic obstructive lesions and gastro-colic and other intestinal fistulae are among the intestinal pathological states predisposing to pellagra. Only infrequently does pellagra develop following gastrectomy or gastro-enterostomy. Symptoms of pellagra commonly accompany the steatorrhoeas. The position of intestinal infestation is not clear in this respect and it is not apparent whether the parasitic disease is the precipitating cause or whether it is a complication of the established pellagrous condition. Bean and his associates observed 17 examples in the subjects of cirrhosis of the liver and 4 in gall-bladder disease.

Surgical procedures, particularly on the gastro-intestinal tract, may precipitate or aggravate pellagra. The pre-operative dietary intake may have been low and the effects of tissue trauma, anaesthesia and post-operative alimentary upset are among the influencing agents in this group. Large doses of dextrose may upset the vitamin balance and the forcing of fluids result in loss of the essential factors in the diuresis produced. In the series of Beans

and his colleagues, gynaecological operations were an antecedent in 13 per cent of 31 post-operative pellagrous states. Reference is also made to the not uncommon relationship between pelvic disorders in the female and predisposition to the deficiency syndrome.

Neoplastic lesions enhance the tendency to pellagra by virtue of their high metabolic requirements and in certain instances by their particular location; the superimposition of infection and haemorrhage may further affect the body nutrition. Thyrotoxicosis, by increasing metabolism, diabetes mellitus by reason of high carbohydrate diet or urinary loss, and diabetes insipidus are the important endocrine disorders in pellagra-production. The gastro-intestinal disturbances of Addison's disease and of hypothyroidism may act in like manner, but generally secondary pellagra is not commonly encountered in diseases of the endocrine system.

An impressive incidence was discovered in congestive cardiac failure attributable to reduced food intake, alimentary upset and increased metabolic rate. The balance of nutrition may be upset by infections, acute or chronic. Radiation sickness, anaemia, haemorrhage and certain drug addictions are other causes listed. Secondary pellagra is not uncommon in chronic psychotics. Alcoholic pellagra is produced by the action of alcohol on the gastro-intestinal tract and by an inadequate dietary intake.

Clinical Features. – The development of pellagra is a gradual process as a rule but the onset may be acute or there may be periodic remissions and relapses. In the very acute cases pyrexia may be present and the patient sinks into a comatose state. Generally the typical example of pellagra demonstrates a long prodromal period of ill-health before the obvious signs of pellagra appear. The symptoms during this phase are variable and somewhat vague. A sense of weakness, fatigability, headache, loss of appetite and weight, dizziness and gastro-intestinal upset are common and may be mistakenly diagnosed as neurasthenia. Frostig and Spies [535] stress the initial nervous symptoms. The patients appear to have anxiety states associated with depressive features. Headaches, generalized hyperaesthesia and sleeplessness are prominent and there is an increased psychomotor drive. In their 60 cases, Frostig and Spies found these complaints to be practically uniform and not related to the original personality of the patient or to his environmental stresses and strains. Changes in character may appear with loss of sense of responsibility and mental confusion.

Established pellagra may be associated with any of the above symptoms but in addition it presents features which are best described with reference to the individual systems From a general

viewpoint the signs are divisible into four groups – the cutaneous, mucosal, alimentary and nervous. Any of these systems may remain apparently unaffected in the developed case.

Cutaneous Manifestations. – These are usually preceded by gastro-intestinal and nervous features and their characteristics are the symmetry, sites, sharp margins and appearance of the lesions. An erythema associated with slight swelling is the earliest sign and there is a resemblance to sunburn. As the condition progresses the redness is replaced by a reddish-brown pigmentation which next gives place to a definite brown coloration. The surface of the affected skin becomes dry and scaliness develops, the scales being of large or small size. Chronic patches show thickening, loss of elasticity and induration, and fissures may appear in the pigmented skin. The border of the lesion is sharply demarcated from the healthy area and fringed by a line of scales – the hyperkeratotic line of Merck. Usually pellagrous skin changes are dry but bullae may form and secondary infection ensue; bullae are particularly prone to appear in acute cases. During the summer months an exacerbation of the dermatological features tends to occur, whereas these may abate or even disappear in the winter season; with each successive appearance the pigmentation becomes more pronounced and may permanently persist even in the treated patient. As the duration of the condition lengthens the involved sites become darker and more thickened or an atrophic process may develop leaving a thin, inelastic, parchment-like area.

The distribution of the skin changes is related to trauma which includes the action of sunlight. Hence, sites of irritation demonstrate the dermatitis which is particularly to be found on the face and neck, the dorsum of the hands and forearms, the elbows, axillae, heels and perineum, the folds under the breast and the inguinal and gluteal folds. In those whose legs and feet are exposed, the dorsal aspect of the foot and lower leg will demonstrate the lesions. The term Casal's necklace is often applied to the manifestations on the neck. Symmetry is characteristic of the dermatitis but asymmetrical and unilateral lesions have been described by Bean *et al.* [536] who point out that any factor increasing skin metabolism, such as heat or infection, or producing chronic stasis of blood in the skin (as for example, varicose veins and scars) favours the localization in the affected area. Local irritation predisposes a particular area and includes agencies such as tight clothing and heat from the fire.

[illegible] lesions may develop in patients who have never [illegible] iolet radiation. Spies [537] showed [illegible] ffected in spite of exposure to sunlight and noted that in 10 patients with pellagra ultraviolet rays

failed to provoke the lesions. Smith and Ruffin [538] hold the opinion that the intensity of the sun's rays is a factor in the seasonal variation of the disease and found that in the majority of instances the cutaneous changes improved when protected from direct solar radiation; these investigators produced dermatitis in 13 of a group of 36 cases of pellagra by exposure to sunlight. Many of the features of pellagra including photo-sensitivity are encountered in some types of porphyrinuria. Beckh and his collaborators [539] stated that increased porphyrinuria is an integral part of the pellagra syndrome and suggested that its presence could be used as an early objective test. Rosenblum and Jolliffe [540] subsequently found that porphyrinuria is not a constant guide to the diagnosis or in the evaluation of therapy in pellagra but it is a manifestation of the coincident existence of hepatic dysfunction. Watson and Layne [541] demonstrated that the chromogen of the reaction described by Beckh *et al.* was also found in normal urine. The evidence available points to the degree of porphyrinuria affording a fair index of the degree of liver parenchymal disorder [542]; in a series of 15 non-alcoholic pellagrous patients, Remington and Leitner [543] discovered normal urinary excretion of coproporphyrin except in 2 cases which were explicable on other grounds.

Examination of the external genitals is important in pellagra. Scrotal dermatitis is common as is vaginitis; the marked leucorrhoea may in itself give rise to eczematous lesions in the area. Vincent's organisms are recovered in abundance from the vaginal secretions.

Pellagra sine pellagra is the description applied to the disease in the absence of cutaneous manifestations. The nomenclature is largely unnecessary since it has been accepted that any of the so-called cardinal features of the disorder may never develop.

Oral Manifestations. – These have been described in the section dealing with the oral structures and include the signs of nicotinic acid and riboflavin deficiency. It need only be added that the pharynx may also be involved in the inflammatory changes.

Gastro-intestinal Manifestations. – The entire length of the alimentary tract may be affected. The patient commonly complains of a burning sensation behind the sternum and in the epigastrium, nausea, loss of appetite, vomiting and diarrhoea or constipation. Dysphagia, abdominal pain and flatulence are other symptoms. Diarrhoea in the pellagrin is of serious import; the stools are often fluid and very offensive, in some cases bearing resemblance to the motions of sprue or dysentery. Achlorhydria is found in about half the cases and may be histamine-fast and permanent. Diaz-Rubio and Roldan [544] carried out radiological studies in 255 patients with pellagra and the most noteworthy finding was diminution of gastric peristalsis, which often produced marked dilatation and

retarded evacuation of the stomach. Gastric mucosal atrophy was observed in 67 per cent of the cases. In the intestines inflammatory changes, large collections of air and retention of the barium in the terminal loops of the ileum were observed. Spies *et al.* [545] noted that the gastric lesions as viewed by the gastroscope were analogous to those of the mouth. Fisher [546] examined 17 pellagrins complaining of dysphagia by oesophagoscopy. The mucous membrane was intensely hyperaemic and in some cases oedematous, with multiple, tiny ulcers in nine.

Mental Manifestations. – Some of these have been referred to in the consideration of the prodromal features of pellagra. There is a very wide range in the degree of their severity and whereas 'neurotic' symptoms are usually among the earliest, a maniacal outburst or some other form of psychosis may mark the clinical initiation of the disease. Insomnia, anxiety, irritability, apprehension, confabulation, intolerance to noise and motor restlessness may be present and progress to a confused, stuporose, depressed or agitated state. Hallucinations may be prominent and paranoid delusions are not uncommon. The protean nature of these manifestations renders the presentation of a characteristic picture of the mental derangements a difficult matter and the diagnosis may be obscure in patients in whom no other signs of pellagra are evident. Diagnosis may be established by the therapeutic test since nicotinic-acid administration promotes rapid relief. While pellagrins may be admitted to mental institutions on account of misconception of the underlying cause, pellagrous symptoms may be superimposed on an existing psychosis because of the patient's refusal of food and excessive motor activity.

Neurological Manifestations. – Common subjective neurological phenomena are paraesthesias, headaches, cramps, pains in various parts of the body and muscular weakness. Any portion of the nervous system may be affected in pellagra and the degree of involvement varies from case to case, as does the rapidity of onset and progress. A peripheral neuritis may be the presenting lesion and is associated with burning sensations in the hands and feet, muscular asthenia and wasting, hypotonicity, ataxia, and reduction or loss of the reflexes; the lower limbs are predominantly involved and objective sensory changes are usually slight. Involvement of the spinal cord is expressed by evidence of spasticity, ataxia and signs of an upper motor neurone lesion. Combinations of peripheral nerve and spinal cord lesions are found demonstrating different intermediate grades of the two types of lesions. Involuntary movements have often been described; tremors, chorea, or athetosis have been recorded and in some the movements are reminiscent of those of Parkinsonism, the other features of which – mask-like

facies, cog-wheel rigidity, akinesis, generalized flexion – may co-exist. A characteristic facial aspect has long been appreciated as a frequent concomitant of pellagra. The face is expressionless and doleful, there is an apathetic stare from the eyes and the patient smiles but rarely; it is not probable, however, that this is attributable to a lesion of the basal ganglia. Any of the cranial nerves may be affected but this is of infrequent occurrence. Diminution or loss of the sense of smell, tinnitus and deafness, retrobulbar neuritis and optic atrophy and a salty taste in the mouth (in Italy the disease is sometimes referred to as 'salso') have all been reported on occasions. There are no abnormal findings in the examination of the cerebrospinal fluid.

Other Manifestations. – The anaemia of pellagra is considered under the section on blood. Oedema may appear. There may be burning micturition and albuminuria. Loss of libido is frequent and menstruation may cease or become scanty. The blood pressure tends to fall and electrocardiographic abnormalities are frequently discovered.

Pathology of Pellagra

At autopsy the degree of emaciation is variable and may be little in evidence. In long-standing cases emaciation may be profound and a general atrophy of the organs be detected. The skin shows parakeratosis of the superficial layers while the blood vessels of the dermis are involved in a hyaline degenerative change; a lymphocytic infiltration can be discerned with increased pigment in the stratum granulosum and blockage of the hair follicles with dried sebum In other instances an atrophic state of the skin may replace the above appearances of chronic inflammatory change. The lining membrane of the gastro-intestinal system is inflamed or atrophic; ulceration may be superimposed on the congestive oedema of the mucosa which may be covered with a fibrinous membrane. Fatty degeneration of different degrees is evident in the liver and degenerative lesions visible in the kidney. Little of an abnormal nature may be found in the examination of the nervous system, changes in which tend to develop only at a late stage. In the cerebral cortex there may be a striking reduction of the ganglion cells, and nuclear alterations and disappearance of Nissl bodies in others. The frontal lobes usually show the maximum degree of involvement. Within the spinal cord symmetrical, scattered lesions may be demonstrable in the lateral and posterior columns, associated with myelin degeneration; the cells of Clark's column may also be affected There is some resemblance to the pathological picture of subacute combined degeneration of the

cord. The cells of the posterior root ganglion demonstrate chromat lysis. Demyelination of the peripheral nerves may be seen, t distal portions tending to be least affected. Degenerati lesions of the blood vessels of the central nervous system a described.

Treatment of Pellagra

Except in mild cases it is advisable to admit the patient to hospi where adequate supervision and careful nursing can be adopte When pellagrins are put to bed their disease will temporarily benefited even if no other measures are instituted. Cure can obtained if the disease is not too far advanced when some of tl lesions may be irreversible. A well-balanced diet should be pr scribed but it may be necessary gradually to improve the consum tion of food in the presence of severe oral pain, dysphagia gastro-intestinal upset. Yeast and injections of liver extract are great value as are wheat-germ and preparations of hog's stomac Should a macrocytic anaemia exist large doses of liver are indicat and dilute hydrochloric acid is beneficial in the presence achlorhydria. Nicotinic acid may provoke troublesome vasomot reactions and the amide is preferable. The dosage will vary wi the severity of the case. Nicotinamide will produce a response i the skin and mucosal lesions and in the mental changes. Pellagra a multi-vitamin-deficiency disorder so that other essential nutrien are necessary; moreover the sole exhibition of large doses of or vitamin may be attended with adverse results. Riboflavi administration will cure the labial manifestations and certain the skin lesions and thiamin should be supplied for the neurologica symptoms. These vitamins should all be prescribed at the sam time to avoid a state of induced vitamin imbalance. Pyridoxine i valuable for the relief of muscular weakness. Spies *et al.* [547 reported dramatic relief of this feature, which had persisted afte vigorous therapy with the above three vitamins, within four hour of an intravenous injection of 50 mg. of pyridoxine. Vitami supplements should be given by the intravenous route as th occasion demands and in such cases they are best administered i divided doses during the day. Spies [548] employs a formul containing 50 mg. nicotinamide, 10 mg. thiamin, 5 mg. riboflavi and 75 mg. ascorbic acid. If the pellagra is severe, he prescribe 150 mg. nicotinamide thrice daily; 4 to 6 oz. of dried brewers yeast or oral liver extract, or 150–300 grammes of wheat-germ ar given daily or, as an equally effective measure, 3 or 4 doses o 20 c.c. of parenteral liver extract. It is important to continu treatment for a sufficiently long period since premature cessatior

may be followed by relapse. Prophylactic measures should be advised after cure of the malady.

Symptomatic treatment is ordered as required. Mouth-washes for the oral lesions, protection of the skin from sunlight and appropriate applications for the dermatitis and astringents or opium for the diarrhoea should be employed. Iron is administered if indicated by the blood examination and sedatives may be necessary for the mental upset.

ADULT SCURVY

THE CONDITION of scurvy appears to have been described by Hippocrates and since then numerous references to it are to be found in the writings of mariners, colonists, soldiers and physicians. The experiences of James Cook are noteworthy in the elucidation of the disease and the works of Lind [549] and Hess [550] are important landmarks. Lind considered that scurvy was attributable to lack of fresh vegetables and advocated oranges and lemons as anti-scorbutic agents. Consumption of lemon juice was made obligatory in the British Navy in 1795 due to the efforts of Sir Gilbert Blane. On land, outbreaks of scurvy have been reported during several wars and particular prevalence of the disease has been observed in Northern States where vegetation is poor, and in countries where the crop has failed.

Aetiology. – Deficiency of ascorbic acid is the cause of scurvy. Experimental evidence, analysis of the dietary content of vitamin C in epidemics of scurvy and the curative effects of the vitamin have all served to confirm this conclusion. Since man is unable to synthesize vitamin C he is wholly dependent for his supply on food sources. McMillan and Inglis [551] analysed a series of adult cases of scurvy in Britain. Of 53 patients, 48 were males and 5 females, and the ages ranged between 41 and 82 years. Fifty-one lived alone, 28 in working-men's hostels; 48 cooked for themselves and there was an inadequate financial income in the large majority. The intake of potatoes and vegetables was low in all cases. The authors assessed the causes of scurvy in their group as ignorance, apathy and poverty. 'Bachelor's' and 'widower's' scurvy are terms commonly employed and the condition is relatively frequent in those who live alone and cook their own meals. Improper understanding of the elementary principles of dietetics may exist in mentally deficient subjects in whom the disorder may appear. The therapeutic employment of special diets in which the vitamin-C content has been inadequate for minimal requirements has produced scurvy, and particularly culpable in this respect were many of the diets formerly prescribed for patients with peptic ulcer. Infection by increasing the demands for vitamin C may precipitate scurvy, and trauma may also be a factor in its production. Large amounts of vitamin C may be lost in the stools in diarrhoeal states and gastro-intestinal dysfunction in general may be accompanied by diminution in ascorbic acid intake. There has been so marked a reduction in the incidence of scurvy that frank scurvy now is an

uncommon disease, but the milder forms are probably quite prevalent although they may readily escape recognition.

Pathology. – The pathology of scurvy is that of vitamin-C deficiency so that the essential derangement is to be found in the intercellular substance. The changes have already been described, but suffice it to point out that the blood vessels present the sites of maximal injury. Fluid, often blood-stained, may appear in the serous cavities and the tissues may be oedematous. Growth exerts a modifying influence and while in the child osseous manifestations are prominent, similar changes are not obvious in adult scurvy. The teeth of adults are involved and the dentine is absorbed and becomes porotic, this process first appearing about Tome's canals; the little dentine which is formed is inferior in quality [552]. The pulp is also affected and may show congestion and oedema or atrophic changes. Degenerative lesions occur in the odontoblasts and areas of cystic formation and calcification may appear.

Clinical Features. – The onset of adult scurvy is insidious and the early symptoms are non-specific. A general loss of vitality, undue fatigability and breathlessness following mild exertion are among the usual preliminary symptoms. A disinclination for physical exertion is noticeable, and the mental activities may be reduced with the appearance of alterations of temperament such as anxiety, depression and negativism. These features may persist for months without the development of other clinical evidence of the underlying vitamin-C-deficiency state. The face becomes bloated and the complexion is sallow or muddy. Pains in the legs and arms are common after exercise, the calves being particularly affected.

The signs which subsequently develop can largely be grouped under skin changes, gingival lesions, haemorrhages and alterations of the blood picture In the experimental production of vitamin-C deficiency in man, Crandon, Lund and Dill [553] observed as the first sign of clinical scurvy small, perifollicular, hyperkeratotic papules situated over the buttocks and posterior aspects of the thighs. Fragmentation of the hairs was noted at about the same time. Each papule contained an ingrown hair. An associated dryness of the skin, most pronounced over the extensor surfaces and over the dorsal aspects of the hands, was also evident. The papular condition corresponded closely to the follicular hyperkeratosis of vitamin-A deficiency. An important aspect of the skin haemorrhages is their situation about the hair follicles. Their size varies greatly The initial evidence of skin haemorrhage is generally present in the legs, where the haemorrhages are also most numerous, but pressure or trauma will effect their appearance at any site; characteristically the face, palms, soles and medial aspects of the thighs are spared. Haemorrhage into a muscle produces a brawny,

indurated, tender swelling. Epistaxis is not infrequent and haematuria may be recognizable macroscopically or microscopically. In advanced stages bleeding can involve any organ and irritative or paralytic phenomena ensue if the central nervous system be the seat of the haemorrhage. Unlike infantile scurvy, subperiosteal haemorrhage is uncommon. As the disease progresses, the haemorrhage, which in the earlier phases was merely a capillary oozing – although very large collections of blood could result – tends to arise from larger vessels. Haemorrhagic effusion into the pericardial or pleural sacs may occur. The oral lesions of scurvy are of relatively late onset and in the experiment of Crandon *et al.* were observed only after six months when there was but slight bogginess of the gums; these investigators demonstrated occasional discontinuities in the lamina dura. Only when the teeth are present will scorbutic gingival lesions develop and the state of the dental hygiene will influence the time of their initial appearance and the rapidity of their progress; the changes are more prominent around deformed or broken teeth. With the longer duration of the scurvy, the gums become swollen and boggy and oozing of blood will follow even slight pressure or trauma. The gingival enlargement may become so pronounced that it hides the teeth. Ulceration, infection and even gangrene may ensue. It is at the inter-dental papillae that the gum changes begin. Mastication is difficult and painful and may aggravate the ascorbic-acid deficiency by further reduction of food intake. The teeth are loosened and may spontaneously become detached from the jaws. Absorption of the alveolar margins of the upper and lower jaws is associated with the dental abnormalities. Kruse [554] claims that biomicroscopic examination of the gums provides a satisfactory method for assessment of the vitamin-C status of the individual and Slobody [555] found close agreement between the results of the intradermal vitamin-C test and the gum condition.

Among the other manifestations of adult scurvy are oedema of the lower limbs, cardiac dilatation and distress, vasomotor collapse and anaemia. The face in pronounced scurvy may become brownish and even deeply pigmented. Localized oedema is evident over more deeply seated haemorrhages. Fever is common and the pulse is rapid and weak. The patient is prone to infection and suppuration may develop in any localized extravasation of blood. The healing of wounds is impaired. In the absence of treatment scurvy shows a steadily progressive course with a fatal outcome, death ensuing from infection, haemorrhage or cardiovascular collapse. The haematological changes of vitamin-C deficiency are discussed in the section on vitamins in haematology.

Diagnosis. – Diagnosis of scurvy is based on a history of insufficiency of ascorbic acid consumption or of circumstances

leading to increased requirements and on the clinical features of the disorder. The well-developed picture can readily be recognized but the minor grades may require the employment of special diagnostic measures. Particular difficulty is encountered in the so-called subclinical scurvy, but the criteria for this condition appear to vary with different investigators. Different standards are accepted and it is well to point out that a state of the body reserves below that of saturation levels is not necessarily indicative of a prescorbutic condition; nor does the urinary excretion of vitamin C or the plasma ascorbic acid level afford irrefutable evidence of hypovitaminosis C – both may be low in the presence of no impairment of health. The various tests available for the diagnosis of vitamin-C deficiency have been described in the chapter on vitamin C.

Treatment. – Vitamin C may be administered in the treatment of scurvy either in the crystalline form or in the natural form, usually as fruit juices. While Ralli and Sherry [552] have given as much as 6 grams of the crystalline form with no untoward effects, the parenteral route is only called for when gastro-intestinal upset interferes with ingestion or absorption of the vitamin. These authors point out that relatively small amounts will clear up the symptoms of scurvy but large doses are required to saturate the tissues, and that these may show considerable variation in different subjects; the quantities for the latter purpose they found to range in their patients from about 800 to 23,300 mg. of ascorbic acid. The amount required, they state, is proportional to the degree and duration of the deficiency and to the method of administration. If smaller daily doses are administered the total quantity necessary is greater than if larger doses are given. Once an individual has had scurvy it is not sufficient to saturate the tissues with one massive dose; to maintain a state of saturation a larger daily intake of vitamin C is necessary than that required in the normal subject. The dose of ascorbic acid when the parenteral route is used is somewhat smaller than the oral dose and intramuscular injection is preferable to intravenous. A few cases have been recorded in which the scorbutic patients proved resistant to oral vitamin-C treatment but responded when the vitamin was supplied by the parenteral route.

The gum changes show a remarkable response within a day or two and are usually almost normal within a week in acute scurvy. Dental treatment should be adopted simultaneously with vitamin-C therapy. Succeeding the improvement of the gums the mental impairment is relieved, then the haemorrhages and lastly the skin discoloration. As has been stressed elsewhere, vitamin deficiency disease is practically never restricted to lack of a single vitamin, so that other existing deficiencies require simultaneous correction.

RICKETS – OSTEOMALACIA AND ALLIED DISORDERS

RICKETS

RICKETS (RACHITIS, the 'English disease') is a disorder of calcium and phosphorus metabolism due, except in rare instances, to lack of vitamin D. The origin of the term 'rickets', introduced by Daniel Whistler in 1645, is somewhat obscure. Some derive it from the surname of a quack reputed to have been the first to treat the condition; others trace it to 'rucket', which in Dorset dialect signifies shortness of breath. Not until 1650 did the condition become generally recognized as a result of the report of a committee headed by Francis Glisson. That credit was denied to Whistler for his work on the subject was due to his personal character and reputed dishonest activities.

Aetiology. – Many theories were advanced before the true nature of the cause of rickets was established. No evidence of an hereditary influence was presented, and it became obvious that children reared under similar circumstances showed different susceptibilities to the disease. It is not easy precisely to explain this varying susceptibility, but certain factors are now appreciated. Prematurity predisposes to rickets, for most of the calcium of the foetus is deposited in the last two to three months of intra-uterine life. The maternal dietary content of calcium and vitamin D greatly influences the density of the foetal bones, and the chances of the development of rachitic disease in the infant are increased if the mother's diet is deficient in these substances. Incidental disease, such as infections and gastro-intestinal disturbances, may also predispose to rickets in the individual case, although the theory of an infective origin for the disorder has been refuted. Seasonal changes play an important part since they limit the opportunities for exposure of the body to solar ultraviolet radiation. Consequently it is not surprising to find that the peak period of incidence of the disease is March and early April. The effective rays have a wave length of between 2,600 and 3,150 Angstrom units, and the filtering action of dusty or smoke laden atmosphere, together with the obliquity of the rays in northern latitudes, result in a marked reduction of these rays during the winter months. Skyshine offers considerable antirachitic properties. The geographical distribution of rickets is in close correlation with deficiency of sunshine, though the disease is very rare in the far north where fish is the staple diet. Tropical and subtropical areas show a paucity of cases, unless the purdah habit is practised or the diet is very deficient. Deeply pigmented individuals, such as negroes, residing in temperate zones,

derive less benefit from the limited available sunshine because of the protective influence of their pigmentation. Dietary factors play a significant rôle, since, apart from the action of sunlight on the body, they are the only naturally available source of vitamin D. Irrespective of the vitamin-D content of the diet, the nature of the ingested foods influences calcium metabolism. Deficiency of calcium intake is of particular importance in regions where under-nutrition and famine are prevalent. Lack of balance between the calcium and phosphorus concentrations of the diet and disproportionately large quantities of carbohydrate exert a similar action, *although those carbohydrates yielding organic acids increase* calcium absorption; in adult subjects protein promotes a beneficial response to the absorption and retention of both calcium and phosphorus, while a high fat diet is likely to be particularly rich in the fat soluble vitamin D. Foods rich in oxalates are detrimental, calcium oxalate being precipitated in the alimentary tract and rendered unavailable to the animal body. Cereals, especially oats, are rachitogenic; the responsible agent is phytic acid. The association of rickets with growth is generally recognized, and when growth ceases because of marasmus, infection or other disorder, there is usually cessation of rachitic activity. It is essentially a disease of active growth, children between four months and two years being particularly susceptible; the rapid growth of premature infants is an additional factor in their predisposition to rickets. Fresh air and exercise in themselves have no place in the aetiology of rickets.

Types of Rickets. – Rickets is especially a disease of infancy, but may first appear or recur during later childhood and in adolescence. When the first manifestations present themselves after the age of four, the term 'late rickets' (rachitis tarda) is applied. Foetal rickets is a rare disorder in which the features of the disease are present at birth; it may occur in the offspring of mothers suffering from osteomalacia or from marked nutritional deficiency. Its infrequency is explained by the calcium content of the foetal skeleton accumulating at the expense of the maternal stores. Bone is predominantly composed of salts of calcium and phosphorus, and interference with the absorption, utilization or assimilation of these two elements will be reflected in disturbed bony development. In this respect two distinct varieties of rickets are encountered – coeliac rickets and renal rickets. Hepatic rickets is extremely rare and follows prolonged hepatic disease. Scurvy rickets merely implies the simultaneous presence of scurvy and rickets.

Pathology. – Normal growth in long bones occurs by endochondral ossification. The cartilage cells on the epiphyseal side proliferate continuously, while the mature cells adjacent to the diaphysis

undergo degenerative changes and are subsequently replaced by capillaries and osteoblasts which deposit the bony matrix within the spaces previously occupied by the cartilage cells. In normal growth there is, on the diaphyseal side of the narrow epiphyseal cartilage, a continuous straight layer of clear or empty cartilage cells, one or two layers deep. The first histological evidence of rickets is the cessation of the degenerative change in the mature cartilage cells in whole or in part of the layer of clear cells, and a resulting absence of ingrowth of osteoblasts and a disordered invasion of capillaries. The matrix between the undegenerated cartilage cells does not undergo calcification [556]. Wolbach states that mild degrees of rickets are evidenced by a moderate increase in the width of the epiphyseal cartilage, which presents an irregular border at the diaphyseal side, and in more advanced stages the osteoid material increases in amount in accord with the duration of the disease. The epiphyseal cartilage columns, normally clearly aligned, become irregular, and the persisting cartilage cells spread into the shaft, so that the normal regularity of the epiphyseal line is lost. Osteoid remains uncalcified and becomes readily distorted in the direction of the forces applied because of its lack of rigidity. Its amount is proportional to the duration of the metabolic defect, the degree of increase in width of the epiphyseal cartilage reflecting the period of existence of the rachitic state. The cancellous bone of the diaphysis and the cortical bone undergo marked resorption, and deposition of osteoid tissue under the periosteum occurs. Osteoclastic destruction of bone continues normally. Periosteal bone formation proceeds at an enhanced rate, and the diameter of the long bones may be increased, but, as in that of endochondral origin, such bone is deficient in calcium content. Bony rarefaction, deformities and retardation or cessation of growth are manifested. The parathyroid glands are hypertrophied in rickets.

Clinical Features. – Usually the first symptom of rickets to attract the attention of the mother is excessive perspiration, particularly on the head, neck and upper thoracic region. The degree of sweating may be great enough to be visible as beads on the forehead and to moisten the pillow. Sleeping and exertion augment the severity of the perspiration. Sweat rashes not uncommonly appear. The child resents being lifted, and may cry when moved, but generally there is no marked degree of tenderness unless scurvy co-exists. A lack of spontaneous movements of the limbs may be evident, and walking may produce pain. Restlessness may be marked, especially at night, and the child throws off the bedclothes even in cold weather. Head rolling can be so pronounced that the hair is thinned or worn away completely at the affected site. Irritability, loss of

appetite and pallor may develop. Muscular hypotonicity and weakness are demonstrated by the child's inability to hold its head up, sit up and walk at the usual age. Loss of tone in the muscles and laxity of the ligaments may allow an abnormally wide range of passive movements of the limbs and spine at their articulations (acrobatic rickets). Gastro-intestinal disturbances and respiratory infections are not infrequent complications. Dentition is delayed; the teeth do not appear in their normal order and may erupt singly instead of in pairs. Anaemia, attributable to general malnutrition, is commonly present.

Among the nervous manifestations are laryngismus stridulus, tetany, convulsions and spasmus nutans. Laryngismus stridulus is found in the first two years of life and is due to a spasmodic closure of the glottis, the vocal cords being strongly adducted. Respiration is suddenly arrested and the frightened child remains immobile, the face rapidly becoming cyanosed. Most often the attack lasts only a few seconds, and its cessation is indicated by a loud crowing inspiration. In some cases consciousness is lost, and in others a convulsion ensues. The convulsion may be generalized and indistinguishable from that of other aetiology. The fits may be of very frequent occurrence and may appear in serial order. Occasionally only one side of the body is affected in the seizure. An attack may end in death, or the bout may be very mild, involving only a brief respiratory distress followed by a scarcely noticeable crowing noise. On occasions a slight degree of inspiratory stridor may persist for about half an hour. Emotion is a recognized precipitating factor. The condition is a manifestation of spasmophilia. The frequency of attacks is very variable and numerous seizures may appear in the twenty-four hours Spasmus nutans is of uncommon occurrence. The disorder occurs in children usually between the ages of 3 and 18 months, and is rarely encountered after the second year of life. Involuntary rhythmic movements of the head are associated with nystagmus. The head movements are of small amplitude and occur at the rate of about 20 to 40 per minute; they are continuous and not spasmodic, and may appear as lateral nodding, rotatory shaking, or to-and-fro movements. They cease when the eyes are closed and when the child is lying down. The nystagmus presents certain peculiarities. It increases if the head is held firmly between the hands Frequently the nystagmus is more pronounced in one eye, or it may be confined to one eye only. It is rotatory or lateral in type, although the direction of the nystagmus may differ in both eyes. The ocular movements are seen when the head is unsupported, and may be absent when the head is resting on the pillow. A disturbance of the co-ordination between the muscles of the neck and eyes constitutes the functional basis of the

disorder, the condition persisting for but a few weeks as a rule. Bad lighting is a contributory cause, so that spasmus *nutans* is encountered usually in the winter months or late fall.

Tetany is a symptom complex whose manifestations originate in an increased irritability of the neuromuscular system. The biochemical changes allow of separation of the syndrome into two main groups – the hypocalcaemic and eucalcaemic varieties. An unusual type is attributable to a deficiency of magnesium; an example was described by Millar [557] in a child of 6 years of age who suffered from Legg-Perthe's disease and in whom the blood magnesium level fell to 0·6 mg. per 100 c.c., but, following two weeks' therapy with magnesium sulphate, it rose to 2·6 mg. per 100 c.c. In the hypocalcaemic group the concentration of the serum calcium is decreased, and among the causes are rickets, the steatorrhoeas, hypoparathyroidism and renal disease. The eucalcaemic group is considered to arise from a reduction of the amount [illegible] of excessive amounts of alkalis. Tetany in childhood is most commonly encountered in active rickets. Holt and McIntosh [558] found only 3 out of 293 cases of infantile tetany which failed to show definite signs of rickets. From a clinical standpoint tetany may be divided into latent and manifest forms. In the latent form the hyper-excitability of the neuromuscular system can be evidenced by mechanical or electrical stimulation of the nerves. Chvostek's sign is elicited by tapping the trunk of the facial nerve just below the zygomatic process and immediately in front of the external auditory meatus; a brief contraction of whole or part of the facial musculature on that side indicates a positive response. Its value is greatest after the first week of life and before the fifth year. It is a quantitative reaction, for even a normal nerve will produce a similar reaction if the percussing force is sufficiently severe. Similar muscular reaction may succeed the tapping of the peroneal nerve where it winds round the head of the fibula, and the ulnar nerve at the elbow. Trousseau's phenomenon develops when pressure, sufficient to obliterate the radial pulse, is exerted on the blood vessels and nerves of the upper arm by a tourniquet or the cuff of a sphygmomanometer. A typical carpal spasm denotes a positive sign, and both hands may be affected by it during the procedure. Trousseau's phenomenon is much less reliable than Chvostek's. Carpal spasm may also appear when the arm is forcibly abducted. Dimpling of the tongue may follow its percussion. Erb's phenomenon exhibits the capacity of the neuromuscular system in tetany to respond to galvanic stimulation by a current weaker than that required to produce a response in

the normal subject; the results may show spontaneous variation from day to day in the same child, and different examiners may obtain different readings, so that care must be exercised in the interpretation of the results. Manifest tetany includes laryngismus stridulus, convulsions and carpo-pedal spasms. Only a small percentage of rachitic children show these manifestations of tetany. The development of the spontaneous features of tetany is not uncommonly preceded by an acute infection. In an attack of carpo-pedal spasm a characteristic position of the hands and feet is assumed. The hand is stiff, the fingers extended at the inter-phalangeal joints and partially flexed at the metacarpo-phalangeal joints, the thumb is markedly adducted so that it comes to lie under the other fingers, and the wrist and elbow are flexed; the term 'main d'accoucheur' has been applied to this posture of the hand. Pedal spasm produces extension of the feet and flexion of the toes, and the plantar surface of the soles becomes markedly concave; the position is similar to an equinovarus deformity. The onset of carpo-pedal spasm is sudden, though it may be preceded by paraesthesias of the parts. In a severe bout pain may be pronounced. The functional disorder may persist for days, although during this time the severity of the tonic spasm varies. In such prolonged instances oedema sometimes appears over the dorsum of the hands and feet. The musculature of other parts of the body may be affected by a similar process. Facial spasm produces a fixed expression – the 'tetany facies'. Rigidity of the whole body appears in severe cases, and difficulty with respiration and swallowing may be experienced. The sympathetic nervous system and involuntary musculature are involved in some cases, and sudden death, attributable to cardiac tetany, has been described.

The osseous lesions of rickets vary with the age of the child. Those bones which show the maximum rate of growth at the particular period in question will be most severely affected. At 3 to 4 months the rapid growth of the head predisposes the infant to craniotabes. Enlargement of the costochondral junctions makes its appearance at about 6 months, and later in the first year enlargement of the epiphyses becomes evident, being best seen at the lower end of the radius. The stresses imposed by posture are of great importance in determining the shape of the deformities. Craniotabes is a softening of the occipital and parietal bones, so that the examining finger is able to indent the affected portion; the contention that similar changes may develop in normal children who show a rapid rate of growth has been advanced by some authorities, and follow-up of such children has revealed no evidence of a rachitic origin for the skull changes. The rachitic head is square-shaped and there is enlargement of the frontal and

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the normal subject; the results may show spontaneous variation from day to day in the same child, and different examiners may obtain different readings, so that care must be exercised in the interpretation of the results. Manifest tetany includes laryngismus stridulus, convulsions and carpo-pedal spasms. Only a small percentage of rachitic children show these manifestations of tetany. The development of the spontaneous features of tetany is not uncommonly preceded by an acute infection. In an attack of carpo-pedal spasm a characteristic position of the hands and feet is assumed. The hand is stiff, the fingers extended at the interphalangeal joints and partially flexed at the metacarpo-phalangeal joints, the thumb is markedly adducted so that it comes to lie under the other fingers, and the wrist and elbow are flexed; the term 'main d'accoucheur' has been applied to this posture of the hand. Pedal spasm produces extension of the feet and flexion of the toes, and the plantar surface of the soles becomes markedly concave; the position is similar to an equinovarus deformity. The onset of carpo-pedal spasm is sudden, though it may be preceded by paraesthesias of the parts. In a severe bout pain may be pronounced. The functional disorder may persist for days, although during this time the severity of the tonic spasm varies. In such prolonged instances oedema sometimes appears over the dorsum of the hands and feet. The musculature of other parts of the body may be affected by a similar process. Facial spasm produces a fixed expression – the 'tetany facies'. Rigidity of the whole body appears in severe cases, and difficulty with respiration and swallowing may be experienced. The sympathetic nervous system and involuntary musculature are involved in some cases, and sudden death, attributable to cardiac tetany, has been described.

The osseous lesions of rickets vary with the age of the child. Those bones which show the maximum rate of growth at the particular period in question will be most severely affected. At 3 to 4 months the rapid growth of the head predisposes the infant to craniotabes. Enlargement of the costochondral junctions makes its appearance at about 6 months, and later in the first year enlargement of the epiphyses becomes evident, being best seen at the lower end of the radius The stresses imposed by posture are of great importance in determining the shape of the deformities. Craniotabes is a softening of the occipital and parietal bones, so that the examining finger is able to indent the affected portion; the contention that similar changes may develop in normal children who show a rapid rate of growth has been advanced by some authorities, and follow-up of such children has revealed no evidence of a rachitic origin for the skull changes. The rachitic head is square-shaped and there is enlargement of the frontal and

plasia. Points in the differential table include the haemorrhagic phenomena of scurvy, the stigmata and positive W.R. of congenital syphilis, the blue sclerotics, character of the skull and X-ray appearances of osteogenesis imperfecta, and the characteristic radiological findings of osteo-chondrodystrophy and of achondroplasia. The appearances of the lower limbs in infants may suggest bowing due to rickets, but often this is merely an expression of the muscular development, and an X-ray examination will reveal straight bones. The susceptibility of the premature infant and twins to rickets is so pronounced that some regard this as almost 'physiological'; nevertheless the changes are preventable by suitable measures. Clinical diagnosis of the early stages of rickets is to a large extent presumptive, since the symptoms are non-specific. In a study of the incidence of rickets in Britain in wartime, Stocks [559] found that out of 604 children diagnosed clinically as having active rickets, only 5·3 per cent showed radiological signs, and he concluded that there was little correlation between the clinical and radiological methods of diagnosis, the former failing to identify half the cases diagnosed radiologically. The various signs employed in this study in the clinical diagnosis were: delayed closure of the fontanelle, craniotabes, enlarged epiphyses at the wrists, enlarged costochondral junctions, the number of teeth and the age at which walking commenced. It is important to realize that while florid rickets is practically non-existent today in Britain, mild forms are by no means infrequent, and that their recognition may present difficulties without the aid of special methods of investigation. Radiography plays an important rôle in this respect, but in the very earliest stages of the disease it cannot establish a diagnosis with certainty; moreover, the earliest X-ray findings are often open to dispute as to their precise significance. Serial X-ray examinations may for some time give little or no indication as to the progress of the disease. In view of these limitations, estimation of the blood phosphatase offers the most valuable aid to diagnosis. An elevation precedes other manifestations of the disease, and its level parallels the activity of the rickets, normal levels being obtained only when the process is finally quiescent. Increased serum phosphatase occurs in diseases other than rickets, but these are of uncommon occurrence under the age of 2 years.

Prophylactic Measures. – While breast-fed children are less liable to develop rickets, breast feeding alone cannot be relied upon in prophylaxis. Any rapidly growing infant is on the verge of rickets and, however fed, should receive a supplement of vitamin D; 400-800 I.U daily of vitamin D are usually sufficient. Premature babies require about twice as much. Marked rapidity of growth is another indication of the need for increased dosage, while, if

satisfactory exposure to sunlight is available, reduced correspondingly. Greatest susceptibilit present in the first months of life, and by the secon full doses of the anti-rachitic agent used should should be continued for three years or more preparations are preferable to cod-liver oil in infant. The danger of the development of lip should be offset by taking precautions against the m the larynx. The expectant mother in good hygien circumstances requires extra vitamin D her child is [illegible] adequat [illegible] especiall [illegible] three months [illegible] should be continued during lactation These sup protect the mother against minor degrees of calcium the skeleton, and enhance the vitamin-D content Krestin [561] found that inadequate and unintell vitamin-D supplements was a common origin of ric covered no superiority of breast over bottle feeding as incidence of the disorder.

Treatment of Rickets – The dosage of vitamin D requ rickets varies with the individual subject It is advisable not less than 2,000 I.U of vitamin D daily, and no 3,000 I.U. for premature infants Exposure to ultraviole mercury-vapour lamp being more effective than the will greatly assist in the cure The optimum usefulness of is obtained only when a liberal supply of calcium and p are administered, and proper treatment implies that the these minerals should be ample Splinting and other me correcting deformities should be adopted without delay, skeletal system protected against unnecessary strain. Faulty should be corrected, and the diet should contain at f carbohydrate and cereals Clinical, biochemical and rad improvement rapidly ensue, and become evident in a f when adequate treatment is given

In 1938 prophylactic treatment by means of massive sing of vitamin D was introduced, and further investigations esta that infants up to 1½ years of age could be protected against during the winter months by a dose of 400,000 to 600,00 Krestin [562] reported protection during a period of six mon 90 out of 93 children under 2 years of age who had receive oral dose of 300,000 I U. of the vitamin dissolved in arachis considers that this amount is sufficient if the child is seen afte beginning of March, but if seen before this time it would be w repeat the dose in three months. Premature infants

showing rapid growth after an illness, may require double this dosage. In the treatment of mild rickets by single doses of 300,000 I.U., and of more severe forms of the disease by 600,000 I.U., results were fairly good, but not as satisfactory as those obtained by daily administration of vitamin D [563]. Toxic reactions appear to be few and insignificant in the reports in the literature, but their possibility must be considered a disadvantage. Special indications for this mode of therapy arise when maternal care cannot be relied upon, and when the child is liable to gastro-intestinal disturbances.

Rachitic tetany, if urgent manifestations are present, is treated by the intravenous injection of 10 c.c. of a 20 per cent solution of calcium gluconate; in less serious degrees the intramuscular route is satisfactory. These methods produce rapid but transient relief, although the injection may be repeated after an hour. Calcium chloride or ammonium chloride in 15-grain doses every four hours by the oral route will rectify the concentration of calcium ions in the blood, and should be discontinued within three days. Vitamin-D therapy should be started immediately, and full therapeutic doses prescribed. When convulsions are present, a sedative, such as chloral hydrate, is called for, and the administration of some form of general anaesthetic may be necessary. Cold applications to the face are usually effective in laryngismus stridulus. Artificial respiration is required in few instances, and intubation or tracheotomy has rarely been called for.

Special Varieties of Rickets

Late Rickets. – Late rickets (juvenile rickets, rachitis tarda) may represent the persistence of infantile rickets, or the disorder may make its first appearance in later childhood. It is comparatively uncommon, and the presence of former rachitic deformities must be distinguished from the active juvenile form. Dark-skinned races are particularly prone to the disorder, but it may represent a degree of resistance to vitamin D, gradations of severity passing into fully developed juvenile osteomalacia. Diagnosis can only be established by demonstration of the radiological and biochemical changes. Those bones showing the most rapid rate of growth at the particular age of the child will demonstrate the rachitic X-ray appearances. The usual symptoms are those of aching pains in the lower limbs and back. Deformities may appear at a later stage.

Refractory Rickets. – Albright, Butler and Bloomberg [564] observed that certain patients developed rickets even when the … ordinarily to prevent … the majority of … ly were required
cases of refractory rickets 50,000 to [illegible] …

to induce healing, but advocated that the dose should be reduce at the earliest possible moment, consistent with a satisfactor response of the disease, to avoid toxic reactions. Several member of the same family may be affected. The condition may be presen from birth, but resistance to vitamin D may appear only in later years. Fluctuation in vitamin-D requirements was noted by Mackay and May [565]; toxic symptoms appeared on a dose which had been well tolerated for fifteen months and a quantity of the vitamin which might be sufficient at one stage proved inadequate at others. They recommended regular examinations of cases receiving large doses of the vitamin, and the frequent assessment of the correct dosage. Seasonal variations in the response of normal individuals to vitamin D were noted by McCance and Widdowson [566]. As much as 1·5 million units daily may be necessary in some instances of refractory rickets. Operative procedures in children receiving massive vitamin-D dosage may lead to the development of toxic symptoms, and particular care is also indicated during periods of immobilization. Changes in the chemistry of the blood, similar to those of ordinary rickets, are found in the active phase, and parathyroid hyperplasia occurs. The underlying defect in the resistance to vitamin D is as yet not understood

Coeliac Rickets – The steatorrhoeas are not infrequently complicated by rickets, which may not develop until later childhood in view of the associated retardation of growth. The lowered level of serum calcium is responsible for manifestations of tetany so commonly encountered in these disorders. Calcium is excreted in the faeces in increased quantity, and only small amounts can be recovered from the urine. The excess faecal excretion is probably due to a decreased absorption from the alimentary tract. The explanation of this diminished absorption can be propounded in one of several ways: impermeability of the intestinal wall to calcium, the formation of insoluble soaps by the interaction of the calcium and fatty acids, and the presence of excess fat in the intestinal lumen, promoting an increased excretion of vitamin D in the faeces Decreased density of the bones may be evident, and a pronounced degree of rarefaction may ensue. Such changes may exist in the absence of obvious radiological rachitic signs at the epiphysis Rickets may only appear with improvement in the intestinal malabsorption, as the rate of growth, previously arrested or markedly reduced, increases. Besides the correction of the basic disturbance in steatorrhoea, the attendant multi-vitamin deficiency tate must be treated, and calcium administered for some time fter therapy is instituted. Large doses of vitamin D may be ecessary for the relief of this vitamin-deficiency state.

Hepatic Rickets. – Hepatic rickets is of rare occurrence. Steatorrhoea resulting from congenital atresia of the bile ducts may operate as in coeliac disease. Gerstenberger [567] described 3 cases of congenital biliary atresia associated with hepatic cirrhosis and rickets. A rachitic process may also ensue in the presence of a biliary fistula, obstructive jaundice or chronic hepatic disease. When these disorders commence in childhood the consequent stunting of growth may not permit of the development of rickets.

Scurvy Rickets. – Scurvy rickets is not a distinct entity and merely implies the incidence of the two deficiency states in the same individual.

Renal Rickets. – Renal rickets, also known as renal infantilism, renal dwarfism, renal osteitis fibrosa cystica and renal osteodystrophy, is the designation applied to the alterations in the bony structures which occur in some chronic diseases of the kidney. It is an uncommon condition, the principal features of which are renal dysfunction, osteoporosis, rachitic-like deformities, failure of growth and anaemia. Boys are more frequently affected than girls, and there is often a familial incidence. The disorder may appear in infancy, but its onset is usually delayed, twelve years being the average age of commencement. The earlier its appearance the greater is the liability to dwarfism, but growth may be unimpaired if the skeletal lesions first develop in late adolescence or adult life; the terms 'renal infantilism' and 'renal dwarfism' may therefore be misleading.

The nature of the kidney disease varies widely and among those renal disorders in which the malady has been observed are chronic renal fibrosis, congenital polycystic kidneys, bilateral hydronephrosis due to congenital or acquired urinary tract obstruction, renal hypogenesis, multiple calculi and massive deposits of cystine in the renal parenchyma. Bony changes are antedated by the renal pathology, and hypertension and cardiovascular lesions are not infrequently present. Essentially, the kidney disease is well established and is of relatively long duration.

The pathogenesis of the alterations of the bones has been explained on the grounds of inability of the kidneys adequately to excrete phosphorus; marked retention of phosphorus occurs in the blood, which leads to an increased excretion of the mineral into the alimentary tract, where it combines with calcium to form insoluble calcium phosphate so that a calcium deficiency state arises. Parathyroid hyperplasia, which may be pronounced, develops as a secondary phenomenon in response to the increased level of serum phosphorus, but does not appear to be a necessary concomitant. Hyperparathyroidism results in phosphaturia, calcinuria, hypercalcaemia and hypophosphataemia, but in the

presence of renal impairment these effects are modified, for the retention of phosphorus in the blood would nullify the tendency to hypophosphataemia; the high serum phosphorus tends to depress the serum calcium, and the excretion of phosphorus via the urine remains low while a larger proportion than normal is excreted in the faeces [568]. The parathyroid hyperactivity when present increases the demineralization of the skeleton. In the case reported by Albright, Drake and Sulkowitch [349] the parathyroids were greatly enlarged, and of a total weight of 11 grams. These authors considered that renal rickets is in reality osteitis fibrosa generalisita, emphasizing the increased bone destruction as against the lack of ossification of newly formed osteoid, but agree that there is some delay in the latter process. Chronic acidosis occasioned by the inability of the kidneys to excrete phosphate, sulphate and other acid metabolites, produces skeletal demineralization and plays an important rôle.

Liu and Chu [569] draw attention to the low calcium content in the diet of their patients; they introduced the nomenclature of 'renal osteodystrophy' which is probably the best of the existing designations The bone changes may be indistinguishable from those of the osteoporotic type of hyperparathyroidism and rarefaction and cystic formation may be pronounced; or the bone changes may simulate those of rickets. However, the condition bears little true relationship to rickets and shows no beneficial response to vitamin-D therapy which indeed may aggravate it. Alkalis are useful since they counteract the acidotic state. Dihydrotachysterol was employed in the cases of Liu and Chu, and increased the intestinal absorption and the retention of calcium. Diets low in phosphorus, rich in calcium and of limited protein content are recommended. The administration of iron proved useful, insoluble iron phosphate being formed and promoting further excretion of phosphorus in the faeces.

The differentiation of renal rickets, so-called, from true rickets is based on the clinical and biochemical findings of renal insufficiency, metastatic calcification and failure to respond to vitamin D. In renal osteodystrophy the serum calcium is usually normal or subnormal and the serum phosphorus increased; the blood phosphatase is generally elevated. Because of the acidosis, symptoms of tetany are rare. A peculiar yellow pigmentation often affects the skin in renal rickets, which tends to become dry and coarse The prognosis in renal osteodystrophy is very poor. The Fanconi syndrome which is sometimes grouped under renal rickets is discussed in the following section.

OSTEOMALACIA AND ALLIED DISORDERS

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OSTEOMALACIA AND ALLIED DISORDERS

Osteomalacia (adult rickets, mollities ossium) is a disorder in

which rickets develops subsequent to the cessation of osseous growth. It is of rare incidence in Britain, the United States and Western Europe, but is endemic in Northern India and in certain parts of China, and occurs sporadically in Eastern countries. The disease is prevalent in those areas where the purdah habit is enforced. Towards the end of, and following the first World War, hunger osteopathy, probably a manifestation of osteomalacia, appeared in Austria, Germany and Poland.

Pathological Features. – The essential morbid process in osteomalacia is an inability of the body to deposit calcium in newly formed bone. Ossification in the adult implies the formation of osteoid tissue and its subsequent impregnation with calcium salts. In this disease the osteoid tissue is imperfectly calcified, and the weakened bones are unable to withstand the forces of pressure. Secondary resorption of the bone matrix proceeds, so that the bone becomes even softer than is found in rickets and shows a greater diminution in its mineral content. The magnesium concentration of the bone may be increased. Pathologically the changes are similar to the lesions of rickets, the rachitic alterations of the epiphyseal cartilages being of course absent. The bone cortex may be reduced to a thin shell, and the marrow spaces are enlarged and the trabeculae decreased. Periosteal thickening may be present with roughening of the surface of the bone. While the number of osteoclasts are within normal range, the osteoblasts are very numerous. Secondary parathyroid enlargement and hyperplasia is a not uncommon concomitant. Softness and flexibility, rather than fragility of the bones, results, so that deformities are much more frequent than actual fractures, although both may occur.

Pathogenesis. – Osteomalacia shows a much greater incidence in women. Pregnancy, with its demands on the maternal nutrients, is a predisposing factor; lactation operates in a similar manner. The disorder tends to appear at an earlier stage and in greater severity in each successive pregnancy. Because of the marked preponderance of the incidence in the female sex and the association with pregnancy, the erroneous conception of the origin of the disease in a morbid condition of the ovary was held for a long time, and oophorectomy was the treatment adopted in many instances. Such beneficial effects as accrued from the operation were probably due to the prevention of the mineral and vitamin loss in further pregnancies. There are generally several aetiological factors in the production of any single case of osteomalacia, but essentially a disturbance of vitamin-D requirements and calcium metabolism forms the basis. In China, Maxwell [570] found that the diet was poor in caloric value, calcium and phosphorus, and contained practically no animal fat; many of the women led an

almost entirely indoor existence and were but seldom exposed to sunlight. The diet of many osteomalacic subjects consists largely of cereals with very small amounts of meat, fat or dairy products. A deficiency of vitamin D arises in the steatorrhoeas, and a picture analogous to osteomalacia may be produced. Chronic diarrhoea and fistulous communications between different segments of the alimentary canal may impair the absorption of the vitamin by virtue of the too rapid progress of the chyme through the intestines. Meulengracht [571] reported an example of osteomalacia following the long-continued abuse of laxatives in the form of sodium sulphate and sodium bicarbonate, which converted some of the calcium in the food into calcium sulphate. Albright, Butler and Bloomberg [572] ascribed the pathogenesis in a case of late rickets to a state of resistance to vitamin D. Decreased acidity of the gastro-intestinal tract and pronounced alterations of the calcium-phosphorus ratio in the diet are important contributory factors.

Osteomalacia may be associated with renal osteodystrophy or develop in two other forms of renal disturbance – tubular insufficiency without glomerular insufficiency (renal acidosis), and the Fanconi syndrome. In the former there is an impaired capacity of the tubules, of unknown aetiology, for the production of ammonia and in the excretion of acid. The increased demand for calcium as a base leads to hypercalciuria and a tendency to hypocalcaemia. Parathyroid hyperplasia follows and will tend to counteract the tendency to a low serum calcium, and will lead to hypophosphataemia. Albright *et al.* [573] state that, in the presence of a normal or slightly low serum calcium level and a low serum phosphorus level, calcium will not be deposited in the osteoid tissue, and osteomalacia will result. Furthermore, potassium, being a base, tends to be excreted in excess and may lead to features similar to those seen in familial periodic paralysis. A high serum chloride and a low serum carbon dioxide content are characteristic of the condition. The reduction of gastric acidity in acidotic states and the consequent decrease in absorption of calcium from the alimentary canal will also influence the development of the bone abnormalities. The effect of vitamin D and an alkalizing salt in treatment is significant, and rapid resolution of the osteomalacia occurs. For the prevention of subsequent bone disease only the alkalizing salt is necessary. In the Fanconi syndrome (de Toni-Fanconi syndrome) the acidosis arises from the excess of organic acids with which the kidney is presented for excretion. It is a non-azotaemic, hypophosphataemic state accompanied by chronic acidosis and renal glycosuria, the organic acids apparently originating from a disorder of amino acid metabolism and from hypoglycaemia.

Two other modes of origin of osteomalacia are referred to by

Albright and his associates. In one the primary defect in metabolism is a propensity on the part of the kidneys to excrete an increased amount of calcium for any given level of calcium in the serum in the absence of an acidosis or hypercalcaemia. The other variety is largely of academic interest and is of a transient nature following the removal of a parathyroid tumour in osteitis fibrosa generalizata.

Clinical Features. – The severity of osteomalacia varies, and the manifestations are proportional to the duration and degree of the metabolic abnormality. Symptoms develop insidiously, so that the condition may escape recognition until well advanced. Among the earliest complaints is pain, which characteristically first appears in the back and then in the lower limbs, the thorax and upper extremities being involved at a later stage. At first pain only occurs following movement of the body, but later it is continuous and aching in character. Muscular spasms and cramps are troublesome, and weakness and atrophy of the musculature follow. Fibrillary tremors may be visible in the musculature. There is tenderness even to light pressure over the affected bones. The lower limbs become weaker and the gait is altered, usually becoming 'waddling' in type. Bony deformities as a rule are first manifest in the pelvis and then in order, the thorax, lower extremities, upper extremities and head. The deformity of the bone will vary according to the direction of the forces transmitted through it. Of all diseases, osteomalacia produces the most extreme deformity of the pelvis. The acetabula and lateral pelvic walls are laterally compressed, the sacral promontory is pushed forwards and the ischial tuberosities are approximated. Such derangements of the pelvic shape are responsible for a high incidence of maternal and foetal death. A common complication of labour is a vesico-vaginal fistula. Softening of the spinal column produces a reduction of the compressing forces on the intervertebral discs which, allowed to expand, produce the so-called hour-glass vertebrae. In certain instances the spine is solely or predominantly affected. Kyphoscoliosis may be marked and reduce the patient's height. The head and neck may actually sink downwards into the thorax. Crushing of a vertebra may ensue after a trivial fall. Walking increases the pain in the lower limbs, the alteration of whose shape as well as that of the upper limbs may be in bizarre fashion. Thoracic deformities, such as depression of the sternum, may embarrass respiratory or cardiac function. Fractures may follow injuries of very mild nature, and in the advanced stages the trauma may be so insignificant that the fracture is apparently spontaneous. No joint changes occur as a rule, but examples of osteomalacic ochronosis have been recorded. In the end, the skeletal changes and muscular weakness are so pronounced that the patient is bedridden and usually succumbs to an intercurrent infection or bed sores.

The natural course of the disease usually extends over several years, but may last only several months. An important aspect of the abnormal calcium metabolism is its neurological manifestations The deep reflexes are exaggerated. Tetany and laryngismus stridulus are not infrequent features, and may be the initial symptoms which draw attention to the disease. Cataract is of frequent occurrence.

Biochemical and Radiological Changes. – The biochemical changes which are found in the developed case of osteomalacia are an increased excretion of calcium and phosphorus in the faeces and decreased excretions in the urine; there is a negative calcium balance. The calcium and phosphorus levels of the blood may be normal or lowered, the commonest finding being a normal calcium and low phosphorus concentration. There is an elevation of the alkaline serum phosphatase. Albright *et al.* [573] recognize three different types of blood findings in osteomalacia: (*a*) those in which compensatory overactivity of the parathyroid is lacking – serum calcium low and phosphorus normal; (*b*) those where a compensatory overactivity of the parathyroid is sufficient to maintain the serum calcium at a normal level. Here the serum phosphorus is low; (*c*) those with compensatory overactivity of the parathyroid, but where this is insufficient to maintain the serum calcium at a normal level. The serum calcium and phosphorus are both low.

Radiological examination reveals general decalcification, thinning of the cortices, dilatation of the medullary cavity, deformities and fractures with little or no callus formation.

Differential Diagnosis – In the diagnosis of osteomalacia several diseases must be differentiated Osteoporosis implies a disturbance of tissue metabolism in which there is a reduction of osteoblastic activity but normal calcification of the osteoid tissue It is not infrequent in bedridden subjects and in the elderly, originating from disuse in the former and from diminution of physiological deposition in the latter, while physiological resorption continues. Hyperthyroidism, by reason of increased excretions of calcium and phosphorus, is often accompanied by osteoporosis. Cushing's syndrome (basophil adenoma of the pituitary gland or hyperfunction of the adrenal cortex) may produce an osteoporosis particularly evident in the vertebral column. In these examples of osteoporosis the calcium, phosphorus and phosphatase content of the blood are normal with but few exceptions. A generalized osteoporosis, clinically indistinguishable from osteomalacia, may result from hyperparathyroidism; the blood shows a high calcium, low phosphorus and elevated phosphatase values. Secondary carcinomatous deposits in the skeleton may exhibit marked osteoclastic activity and an extensive osteoporosis follow; areas of destruction

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linical Features. – The severity of osteomalacia varies, and the nifestations are proportional to the duration and degree of the tabolic abnormality. Symptoms develop insidiously, so that the ndition may escape recognition until well advanced. Among the rliest complaints is pain, which characteristically first appears in ie back and then in the lower limbs, the thorax and upper extremities being involved at a later stage. At first pain only occurs following movement of the body, but later it is continuous and aching in character. Muscular spasms and cramps are troublesome, and weakness and atrophy of the musculature follow. Fibrillary tremors may be visible in the musculature. There is tenderness even to light pressure over the affected bones. The lower limbs become weaker and the gait is altered, usually becoming 'waddling' in type. Bony deformities as a rule are first manifest in the pelvis and then in order, the thorax, lower extremities, upper extremities and head. The deformity of the bone will vary according to the direction of the forces transmitted through it. Of all diseases, osteomalacia produces the most extreme deformity of the pelvis. The acetabula and lateral pelvic walls are laterally compressed, the sacral promontory is pushed forwards and the ischial tuberosities are approximated. Such derangements of the pelvic shape are responsible for a high incidence of maternal and foetal death. A common complication of labour is a vesico-vaginal fistula. Softening of the spinal column produces a reduction of the compressing forces or the intervertebral discs which, allowed to expand, produce the so called hour-glass vertebrae. In certain instances the spine is solel or predominantly affected. Kyphoscoliosis may be marked an reduce the patient's height. The head and neck may actually si downwards into the thorax. Crushing of a vertebra may en after a trivial fall. Walking increases the pain in the lower limbs, alteration of whose shape as well as that of the upper limbs ma in bizarre fashion. Thoracic deformities, such as depression of sternum, may embarrass respiratory or cardiac function. Frac may follow injuries of very mild nature, and in the advanced stag trauma may be so insignificant that the fracture is apparently taneous. No joint changes occur as a rule, but examples of oste acic ochronosis have been recorded. In the end, the skeletal c and muscular weakness are so pronounced that the patient ridden and usually succumbs to an intercurrent infection or be

The natural course of the disease usually extends over several years, but may last only several months. An important aspect of the abnormal calcium metabolism is its neurological manifestations. The deep reflexes are exaggerated. Tetany and laryngismus stridulus are not infrequent features, and may be the initial symptoms which draw attention to the disease. Cataract is of frequent occurrence.

Biochemical and Radiological Changes. – The biochemical changes which are found in the developed case of osteomalacia are an increased excretion of calcium and phosphorus in the faeces and decreased excretions in the urine; there is a negative calcium balance The calcium and phosphorus levels of the blood may be normal or lowered, the commonest finding being a normal calcium and low phosphorus concentration. There is an elevation of the alkaline serum phosphatase. Albright *et al.* [573] recognize three different types of blood findings in osteomalacia: (*a*) those in which compensatory overactivity of the parathyroid is lacking – serum calcium low and phosphorus normal; (*b*) those where a compensatory overactivity of the parathyroid is sufficient to maintain the serum calcium at a normal level Here the serum phosphorus is low; (*c*) those with compensatory overactivity of the parathyroid, but where this is insufficient to maintain the serum calcium at a normal level The serum calcium and phosphorus are both low.

Radiological examination reveals general decalcification, thinning of the cortices, dilatation of the medullary cavity, deformities and fractures with little or no callus formation.

Differential Diagnosis. – In the diagnosis of osteomalacia several diseases must be differentiated. Osteoporosis implies a disturbance of tissue metabolism in which there is a reduction of osteoblastic activity but normal calcification of the osteoid tissue. It is not infrequent in bedridden subjects and in the elderly, originating from disuse in the former and from diminution of physiological deposition in the latter, while physiological resorption continues. Hyperthyroidism, by reason of increased excretions of calcium and phosphorus, is often accompanied by osteoporosis. Cushing's syndrome (basophil adenoma of the pituitary gland or hyperfunction of the adrenal cortex) may produce an osteoporosis particularly evident in the vertebral column. In these examples of osteoporosis the calcium, phosphorus and phosphatase content of the blood are normal with but few exceptions. A generalized osteoporosis, clinically indistinguishable from osteomalacia, may result from hyperparathyroidism; the blood shows a high calcium, low phosphorus and elevated phosphatase values. Secondary carcinomatous deposits in the skeleton may exhibit marked osteoclastic activity and an extensive osteoporosis follow; areas of destruction

100 c.c., and on the third day maximal values were evident, averaging 198 micrograms (851 units) per 100 c.c.; a decrease of the vitamin-A levels then ensued and the average concentration of the mature milk was reached on the ninth and tenth days. The average concentration of carotenoids on the first day of lactation was 241 micrograms per 100 c.c., after which a rapid decrease was noted until the fifth and sixth days, when it began to level off; on the tenth day slightly greater values than those of the mature milk were evident.

The influence of regular administration of cod-liver oil to the mother has been investigated. Dann could discover no increased content of vitamin A or carotene in the mature milk or colostrum of mothers who were receiving cod-liver oil. McCosh *et al.* [580] arrived at a similar conclusion. Hrubetz *et al.* [581] observed that the administration of 50,000 units of vitamin A daily to women from the sixth month of pregnancy produced a statistically significant increase in the vitamin-A levels of the early milk which, however, was not maintained in the later periods. When the dosage of the supplements of the vitamin were doubled, the increase was retained throughout lactation; with daily supplements of 200,000 units of vitamin A the concentration in the milk was three times that of the unsupplemented group.

Variation in the vitamin A and carotene content of cows' milk is well recognized, the greatest fluctuation being occasioned by seasonal changes in the diet of the cow [582]. Lawrence *et al.* state that the average of mean values obtained by various investigators since 1933 was 33 micrograms of vitamin A and 30 micrograms of carotene per 100 c.c. Lawrence and his co-workers accept this average figure, and consider that midsummer milk may be 50 per cent higher and midwinter milk 50 per cent lower. The carotene present in cows' milk is almost entirely beta-carotene, whereas in mature human milk only 30 to 40 per cent of the total carotenoids is carotene [583]. Pasteurization, commercial sterilization and irradiation with ultraviolet rays do not affect the vitamin A or carotene content; no loss follows the process of evaporation or drying of the milk, nor is the vitamin-A activity of these forms of milk reduced by storage in a cool, dry place for over a year [584]. Bovine milk, if of average vitamin-A content, will supply the vitamin-A needs of the infant [585].

Roderuck *et al.* [586] review previous investigations of the thiamine content of human milk and present the results of their own studies. During the first days of lactation, human milk was found to contain little thiamine. The concentration of total thiamine increased throughout the first few weeks of lactation to a value of 14 to 14·7 micrograms per 100 c.c. in mature human

milk. Free thiamine in mature milk was noted not to have a constant value, but gradually to increase during lactation; the mean value for women eating self-chosen diets was 4·7 micrograms per 100 c.c. These authors state that the principal determinant of the concentration of thiamine in human milk is the diet; other factors include the emotional and physical state of the woman.

Lawrence *et al.* [582] from a study of the literature estimated the thiamine content of normal cows' milk as between 35 and 40 micrograms of total thiamine per 100 c.c. Thiamine may exist in milk in the free form and as a cocarboxylase, and these two are also present bound presumably to protein. Some 10 to 25 per cent of thiamine is lost in pasteurization by the holder method, and up to 50 per cent may disappear with sterilization. Evaporated milk may show a loss of 20 to 60 per cent of thiamine, which decreases continuously during storage. Reduction of the thiamine content of cows' milk depends on the temperature at which it is stored, and the value may fall by 46 per cent in twenty-two hours at 37° C. [587]. The thiamine content of milk, especially human milk, is barely adequate; Clements [588] observed a partial thiamine deficiency state in 8 per cent of 150 breast-fed infants. The addition of thiamine to the maternal diet during pregnancy and lactation is reflected in a higher thiamine concentration in the milk.

Coryell *et al.* [589] assessed the vitamin-B-complex values of human milk. The mean nicotinic-acid content of the milk decreased slightly in the first two to four days after parturition, and then rose rapidly; on the tenth day the mean value was 245 micrograms per 100 c.c., and the average content of nicotinic acid in mature milk was 176 micrograms per 100 c.c. in women on a self-chosen diet. Pantothenic acid was found to show a rapid increase, rising from 48 micrograms per 100 c.c. on the first day after parturition to 245 micrograms on the fourth day. A gradual increase occurred to the tenth day, the average figure then being 304 micrograms per 100 c.c. The mean pantothenic-acid content of mature human milk for women on a self-chosen diet was 242 micrograms per 100 c.c. The biotin values were very low for the first five days following parturition, when a gradual increase in the biotin level occurred, to reach an average value of 0·38 microgram per 100 c.c. on the ninth day; the mean biotin content of mature human milk for women on self-chosen diets was 0·82 microgram per 100 c.c. No effect was noted on any of these three vitamins in reference to the duration of lactation, volume of the milk or season of the year. Roderuck *et al.* [590] obtained a riboflavin level in mature human milk of 35·4 micrograms per 100 c.c. for women on self-chosen diets. They discovered that the total riboflavin rose rapidly during the first five days of lactation, and slowly during the next

TABLE

	Vitamin A I.U.	Thiamine mg.	Riboflavin mg.	Niacin (nicotinic acid) mg.	Ascorbic acid mg.	Vitamin D I.U.
Children up to 12 yrs. –						
Under 1 yr.	1,500	0·4	0·6	4	30	400
1–3 yrs. (29 lb., 13 kg.) ..	2,000	0·6	0·9	6	35	400
4–6 yrs. (42 lb., 19 kg.) ..	2,500	0·8	1·2	8	50	400
7–9 yrs. (55 lb., 25 kg.) ..	3,500	1·0	1·5	10	60	400
10–12 yrs. (75 lb., 34 kg.) ..	4,500	1·2	1·8	12	75	400
Children over 12 yrs. –						
Girls:						
13–15 yrs. (108 lb., 49 kg.)	5,000	1·3	2·0	13	80	400
16–20 yrs. (119 lb., 54 kg.)	5,000	1·2	1·8	12	80	400
Boys:						
13–15 yrs. (103 lb., 47 kg.)	5,000	1·5	2·0	15	90	400
16–20 yrs. (141 lb., 64 kg)	6,000	1·7	2·5	17	100	400

Daily Vitamin Requirements in Childhood.

vitamin A in the blood of the mother during the last trimester of pregnancy, but no significant drop in the plasma carotene content during this period They considered the fall in concentration to be attributable probably to the high demands of the foetus; the question of haemodilution also arises in the production of this decrease, since after delivery the blood levels rapidly assume normal values. Lewis *et al.* [607] administered 10,000 units of vitamin A or of carotene daily during the last months of pregnancy, and found that these supplements produced a maintenance of good levels during the last phase of pregnancy. However, the vitamin A and carotene levels of the cord blood were no higher in the infants of this group of mothers than the infants of a group of mothers not receiving the supplements; very large doses of vitamin A had no appreciable effect on the vitamin-A content of the cord blood, although resulting in considerable elevation of the concentration of the vitamin in the maternal blood. Lewis and his co-workers attributed this effect to a foetal regulatory mechanism, rather than to failure of transmission through the placenta. Byrn and Eastman [608] estimated the vitamin-A content of the blood of the umbilical cord of 50 infants, and obtained an average of 91·3 units per 100 c c , as compared with an average maternal level of 106·3 units, no close correlation between the levels in the blood of the mother and infant was noted Straumfjord and Quaife [609] estimated a vitamin-A value for the cord blood of 96 units per 100 c c Premature infants have relatively low reserves of the vitamin in the liver, they tend to absorb fats less efficiently than full-term babies, and show lower levels of vitamin A in the blood [610]. The vitamin-A concentration of the blood of 61 infants on an average diet lay between 15 and 141 units per 100 c.c. [611] Lund and Kimble [612] observed that low maternal blood values of the vitamin may not be reflected in the foetal blood.

Keratomalacia and xerophthalmia are late occurrences in vitamin-A-deficiency states. They are essentially diseases of infancy and childhood Swelling of the eyelids, and a purulent conjunctival discharge appear, and photophobia is marked. Permanent blindness may develop in a considerable proportion of cases. Gastro-intestinal dysfunction is common, and the epithelial changes predispose to infection, so that bronchopneumonia or inflammation of the alimentary tract is the usual immediate cause of death Conditions which are peculiar to the early years of life and which interfere with the absorption of vitamin A and its provitamins are: congenital obliteration of the bile ducts, fibrosis of the pancreas, coeliac disease and cretinism. As a rule the deficiency may be overcome by the oral administration of unusually

large quantities of the vitamin, best prescribed in divided doses. The parenteral route may be necessary.

The work of Warkany and his associates in animals [613] has directed attention to the possible influences of vitamin deficiencies in the mother, yielding malformations in the foetus. Female rats were reared on a special diet very low in vitamin A, and at 3 months were bred to males of the same strain; only 3 of 12 mothers carried their litters to or near term. Developmental abnormalities were found in some of the dead young obtained by Caesarian section. In this respect the findings of Smith [614] are of interest. During the six or seven months which preceded the liberation of North-western Holland, a state of severe generalized undernutrition was prevalent in urban areas. A slight but statistically insignificant increase in congenital malformations was encountered. These findings may not be comparable to those of Warkany, who emphasized the effect of nutritional inadequacy, particularly when it existed in the first weeks of gestation.

Vitamin B_1

The foetus obtains its supplies of thiamine by filtration of the vitamin through the placenta. No concentration of thiamine appears to occur in the placenta, since the levels there are almost identical with those of the maternal venous blood and the blood of the umbilical cord [615]. The amount of thiamine stored in the infant's tissues would appear to be of a small order, and is readily depleted by the anorexia and gastro-intestinal upset so commonly associated with childhood disorders. Thiamine deficiency itself tends to produce similar changes in the digestive system, so that a vicious cycle may be established; vomiting and constipation are not infrequent features of vitamin-B_1 depletion, as are restlessness, irritability and depression. Artificially fed babies are afforded a greater protection against thiamine deficiency than are the breast-fed infants.

Infantile Beriberi

Infantile beriberi is not uncommon in Eastern countries, but is rarely encountered in the Western Hemisphere. A case occurring in England is reported by Allibone and Baar [616]. Congenital beriberi is rare; Albert [617] observed only 4 cases in a series of 514 infants suffering from beriberi. The aetiology of infantile beriberi is considered by many to be a deficiency of vitamin B_1. Stannus [618] and Fehily [619, 620] suggest that the condition is

easily as [illegible], [illegible] from [illegible] lactation which is present in the breast milk; other intermediate metabolites which accumulate in the body as a result of the altered carbohydrate metabolism and appear in the milk may also [illegible]. [illegible] that these products lead to an acidotic state, and [illegible] after the [illegible] of the milk as to render it [illegible], as is shown by the infant's aversion to breast milk while readily accepting cows' milk. The occurrence of the [illegible] depends on the amount of breast milk consumed and on the [illegible] of the infant. [illegible] (1953) recognizes four types, the [illegible], pseudo-meningeal, cardiac and [illegible], but features of all are commonly evident in the individual case. The following description is taken from the reports of Jelliffe. Attacks occur [illegible] after breast feeding and consist of vomiting, diarrhoea, abdominal pain and abdominal distension, or of [illegible] of the neck and extremities and convulsions. The [illegible] from [illegible] in bouts of dyspnoea, cyanosis and tachycardia [illegible] may prove fatal or the features of the [illegible] may develop. Oedema, oliguria, [illegible] and cardiac enlargement appear; the oedema [illegible] date in the various serous cavities [illegible]. The child may actually show an increased weight at this stage. [illegible] is an interesting development and is associated with a peculiar cry which is characteristic. Paralysis of the [illegible], [illegible] the left, is of common occurrence. [illegible]. Abdominal distension is evident. Increased [illegible] pressure is revealed by the bulging fontanelle, and [illegible] of the body and limbs. A characteristic [illegible] in the early stages is described by Jelliffe: the infant is [illegible], flabby and pale. Restlessness and complaint may be marked. The reflexes are very variable and may be unaltered [illegible]. Susceptibility to pulmonary infection is pronounced and is an important factor in the high mortality of the disease. Enlargement of the heart to the right and dilatation of the left auricle may be seen on radiological examination. In the great majority of cases autopsy reveals little to account for the cause of death. The mother may exhibit the signs of adult beriberi, but in many instances these are absent. Infantile beriberi usually has an onset between 3 and 5 months of age, and in the absence of adequate treatment the prognosis is very poor. Treatment must be directed both to the mother and child. The infant should be removed from the breast and fed with cows' milk, to which a supplement of thiamine may be added. Parenteral administration of vitamin B_1 should be given to the infant, and subsequently replaced by the oral route. The vitamin-B_1 status of the mother should also be raised to optimum levels.

Pink Disease

Clements [622] discusses the theories of aetiology of pink disease – a virus infection, toxins derived from the ingestion of the spores of a cereal smut, and a deficiency of vitamin B_1. He considers the vitamin-deficiency theory as improbable in view of the satisfactory state of nutrition of most of the infants when first affected with the disease, which is encountered in many breast-fed children with no other signs of avitaminosis. Forsyth [623] was struck by the points of similarity between the clinical pictures of pink disease and beriberi and pellagra, and was accordingly led to treat the condition with vitamin-B preparations; his results were encouraging. Delattre *et al.* [624], Durand *et al.* [625] and Gretton-Watson [626] about the same time reported good effects on the course of acrodynia from vitamin-B_1 therapy. Large doses of thiamine may be necessary, and the parenteral route may be required [627].

Other vitamins have also been used in the treatment of acrodynia. Tisdall *et al.* [628] observed no response to nicotinic acid, but Gounelle *et al.* [629] reported favourable results from the daily injection of 100 mg. nicotinamide. Forsyth [630] has also employed wheat germ in the therapy of the disorder.

'Infantile Pellagra'

This subject is reviewed by Trowell [631]. Some confusion may exist because of the difference in the manifestations from the adult form and because of the numerous names which have been applied to the disorder. Synonyms are Williams' disease, Gillan's oedema, nutritional oedema with pellagra, pellagroid beriberi, cheveux blancs and kwashiorkor. The disease is due to severe malnutrition and carries a high mortality rate. The important components of the syndrome are oedema, skin lesions, stomatitis, alterations of the hair, irritability and photophobia, perhaps diarrhoea with stools suggestive of sprue, and a pyramidal tract or lower motor neurone lesion affecting the lower limbs. A hypochromic or dimorphic anaemia may be present. Signs of deficiencies of various vitamins may be associated. The aetiology is not clear, but it probably represents a separate syndrome, to which the designation of 'malignant malnutrition' has also been applied. Hughes [632] emphasizes the importance of riboflavin deficiency. The condition is found in many parts of tropical Africa, in Central America, in the West Indies, and sporadically in the United States and China.

The Gillmans [633, 634, 635] have carried out a most important study on this malady. By means of liver biopsies they showed that

See Addendum to this page at end of book.

an intensely fatty degeneration of the liver is an invariable concomitant of infantile pellagra. They assessed various modes of treatment by the examination of serial liver biopsies. Vitamins were found to intensify the accumulation of fat in the liver, and were ineffective in preventing the death of the child. Liver extract, rich in the Cohn Factor, was superior to vitamins, but depletion of fat from the liver was slow despite clinical recovery. Spectacular recovery followed the use of dried stomach, 10 grams daily, in combination with hydrochloric acid, and the fat rapidly disappeared from the liver. Vitamins were considered to be dangerous and contra-indicated in infantile pellagra, and dried stomach is the most valuable therapeutic and lipotropic agent. An interesting suggestion put forward was that in infantile pellagra carbohydrate is converted into fat which cannot be utilized, since the amount of fat in the diet was low, and in spite of this, fat accumulated in the liver and was excreted in large amounts in the faeces.

Congenital Malformations in Rats due to Riboflavin Deficiency

Warkany [636] indicates that in a state of maternal malnutrition the struggle between the foetal and maternal tissues for the essential factors may end in favour of the mother. While gross deficiency of riboflavin may lead to infertility, deficiencies below this level may be associated with congenital malformations. Warkany *et al.* [637, 638] were able to produce a characteristic pattern of congenital defects in the offspring of female rats who were existing on a standard diet deficient in riboflavin. Warkany, from an application of his animal experiments, stresses the importance of the diet in the first three months of pregnancy.

Vitamin C

The vitamin-C content of the foetal blood is higher than the maternal figure The foetus would appear usually to derive its vitamin C irrespective of the mother's ascorbic acid status; however, the foetus does not always obtain the necessary amounts of the vitamin from the mother, and congenital scurvy can occur. Lund and Kimble [639] demonstrated that, following the administration of vitamin C, both the foetal and maternal plasma-ascorbic-acid levels rise, succeeded in a few hours by a drop in the maternal level, while the foetal plasma concentration remains higher. These investigators postulated a free passage of the vitamin from the mother to the child across the placenta, but a limited passage in the opposite direction. McDavitt *et al.* [640] have also advanced

the theory of a one-way selective placental filtration. Barnes [641] confirmed the relationship between the plasma levels of the foetal and maternal ascorbic acid, and found this equally to apply to whole blood. He observed the placental concentrations of vitamin C to be of an exceedingly high order as compared with the blood values, and that the former were also higher than the concentrations present in uterine muscle or umbilical cord blood. Barnes found no indication of any ability of the placenta to synthesize vitamin C, and assays in the placenta of other vitamins gave no comparable results. The relationship observed with ascorbic acid appears to be peculiar to this substance. The greatest concentration of vitamin C was found to lie on the syncytial layer of the villus, a smaller portion residing in the stroma; there was consistently more of the vitamin in the foetal than in the maternal portion of the placenta [642]. Slobody *et al.* [643] performed intradermal tests for vitamin-C assessment, and found that the time for disappearance of the dye was always considerably shorter in the newborn than in the mother.

There occurs a rapid fall in the blood-vitamin-C level after birth, and subsequent to the first week of life the values obtained will depend on whether supplements of vitamin C are prescribed and on the method of feeding, significantly greater amounts being supplied in human than in cows' milk. Artificially fed children must rely for their vitamin-C requirements upon the amount supplied in supplementary form. The practice of not supplying vitamin-C supplementation to the artificially fed infant until several weeks of age is to be deplored; it should be started in the first few days of life. Vitamin C can be given in the synthetic form (20 to 40 mg. a day), or as orange juice, a minimum of 1 oz. a day of the latter being necessary, and after three months this quantity should at least be doubled. Occasional intolerance to orange juice requires its substitution by the synthetic form. Should the vitamin-C content of the maternal milk be low, an ascorbic acid supply to the mother is required to promote an increased level, and it should be given also to the infant to replenish the body reserves.

Infantile Scurvy

Infantile scurvy, or Barlow's disease, affects children usually between 6 and 12 months of age, but may be found in earlier life and even after 3 years of age. It occurs predominantly in the artificially fed infant, and hence was formerly more frequently encountered in the richer classes; it is uncommon in breast-fed babies. Congenital scurvy is a rarity, only a few cases having been recorded.

Essentially, scurvy is the same disorder in all age-groups, but

certain factors decide the clinical manifestations at the particular period of life at which the disease occurs. The presence or absence of teeth, the stage of skeletal growth, and the activities peculiar to the age-group are important factors in this respect. Prior to the development of the obvious features of infantile scurvy, symptoms of the deficiency appear insidiously in the form of a failure to gain weight, loss of appetite and irritability. An inquiry into the nature of the feeding – cows' milk without the addition of vitamin C in some form – will yield the cause of these symptoms common to many other disorders. A common history is that orange juice was offered but was rejected by the infant, or that intolerance to the juice was exhibited. At a somewhat later stage it is noted that the baby resents any handling, and that tenderness of the lower limbs is marked, causing the infant to cry after slight to moderate pressure on the parts. Pallor develops, and the face has a pale, earthy appearance and an anxious expression which changes into a terrified look when anyone approaches the bed. As the condition develops, oedema may be found over the tibial regions, and the legs are held immobile in the abducted position with the knees slightly flexed and the limbs externally rotated This stage of pseudo-paralysis may be confused with syphilitic epiphysitis, poliomyelitis, or fracture. The upper limbs are affected in lesser frequency. Subperiosteal haemorrhage accounts for the pseudo-paralysis Haemorrhages into various other tissues may now become evident. The common site is the muscular system. The haemorrhage may present as an obvious swelling. Proptosis may be a feature, or the haemorrhage may come from the gastro-intestinal tract and, uncommonly, may be intracranial in origin. Examination of the urine will usually reveal the presence of red blood cells, or there may be frank haematuria. The epiphyseal area may be the seat of the haemorrhage, and separation of the epiphysis result.

Unless the teeth have erupted the gums do not usually bleed, but gingival swelling and congestion develop if the teeth are in the immediate pre-eruptive stage. In the skin pressure usually determines the particular location of the haemorrhage. Barlow originally drew attention to the lesions of the thorax; there is a backward displacement of the costal cartilages and sternum, which may be confused with the rachitic rosary. Fractures of the shafts of the long bones may also be encountered While anaemia may accompany the scorbutic condition, its incidence is not constant. Pyrexia is common, even in the absence of infection – the so-called 'scurvy fever'.

Radiological examination reveals abnormalities which are of diagnostic value. At the epiphyseal end of the diaphysis the bone

presents an increased linear density, which often extends just beyond the edge of the bone and is known as the white line of Fraenkel. The immediately adjacent bone lying shaftward shows such a marked decrease in density as to appear absent, and a ground-glass appearance is presented by the remainder of the shaft, although localized areas of rarefaction may be visualized towards the extremities of the long bones. The epiphyses, which are decalcified, may present an unusually sharply defined appearance. Subperiosteal haemorrhages are not radiologically demonstrable in the early stages of the disease, and only when calcium salts become deposited in the effused blood will they be visualized. The X-ray examination offers a means of early diagnosis of infantile scurvy.

Parenteral administration of vitamin C will be necessary only when the oral route is contra-indicated, or in very severe cases. Rapid saturation of the tissues may be achieved with large doses. As a rule 200 to 300 mg. thrice daily will suffice for curative purposes; thereafter a maintenance dose should be prescribed.

Vitamin D

Many of the aspects of the relationship of vitamin D to nutrition in childhood have been described under the section on rickets. The rate of growth, the type of food eaten, and the degree of exposure to sunlight will affect the requirements of infants and children. Premature infants require particular care to avoid a vitamin-D-deficiency state. Human milk by no means offers full protection against rickets, nor will an ample supply of vitamin D compensate for extreme inadequacy of calcium and phosphorus ingestion. As yet it is not apparent why human milk is so much more effective against the development of rickets than is cows' milk; it does not depend on its vitamin-D content *per se*, which is of a low order, nor on its calcium or phosphorus values, which are considerably lower than those of cows' milk. Vitamin-D supplementation should not be delayed, and should be given in conformity with the dosage recommended by the National Research Council. Care must be taken to avoid the development of a lipoid pneumonia when administering cod-liver oil.

Vitamin K

Reports in the literature on the prothrombin level at birth show some disagreement. For example, Quick and Grossman [644] found low values, but these were not evident in the studies of Fitzgerald and Webster [645]. Brinkhaus *et al.* [646] observed

a reduction of the plasma prothrombin level in the newborn, but noted considerable variation in the degree. Sanford *et al.* [647] in 606 plasma prothrombin estimations in the cord blood of normal infants obtained values similar to those of the mothers' blood, but other investigators have discovered lower concentrations. A 'physiological' hypoprothrombinaemia in the newborn usually appears in the second to the fifth day, and this is the period when haemorrhage neonatorum is most likely to occur. The decline in prothrombin is greater and more prolonged in breast than in bottle fed infants [648], and more pronounced in the winter and spring than in the summer and autumn [649]. Magnussen [650] observed lower prothrombin values in premature infants as compared with those of a full-term group, the lowered levels being evident even after two weeks; no significant difference was noted between the maternal blood concentrations of prothrombin of the two groups. Snelling [651] obtained no correlation between the vitamin-K content of the maternal diet and the clotting time of the infants' blood. In the early part of pregnancy the plasma prothrombin falls slightly, rising again after two months to reach a concentration slightly above normal at the end of 16 weeks; another low level is reached at 28 weeks, when there is a steady rise to term [652]. At full term the pregnant woman has a prothrombin value above normal, which is not affected by even massive doses of vitamin K [653].

The cause of the 'physiological' fall in prothrombin in the infant is not clear. Divided opinion exists as to the place of the vitamin-K content of the maternal diet in its production, and another view is that it is dependent on the low intake of milk in the first 24 hours of life. Biosynthesis of the vitamin in the intestines may explain the delay in the establishment of normal values. Rapid return of the prothrombin level will follow the administration of vitamin K to the infant, and if vitamin K is administered to the mother, either during labour or in the few preceding days, there ensues a higher level of prothrombin at birth, which is better sustained in the succeeding days [654]. Toohey [655] states that vitamin K is effective if given during labour at least two hours before delivery.

Considerable controversy has arisen regarding the value of administering vitamin K in the prophylaxis of haemorrhage neonatorum Not all haemorrhages are due to hypoprothrombinaemia in infants; prothrombin deficiency is not present at birth in the majority of infants, so that haemorrhage that occurs at the time of delivery should not enter into this category. Sanford *et al.* [647] failed to find an associationship between the haemorrhages of the newborn and a prothrombin deficiency, nor were these decreased by administration of vitamin K. Potter [656], from

THE VITAMINS IN PREGNANCY

WHILE GROSS nutritional deficiencies in pregnancy are readily recognizable, the minor degrees of malnutrition, which are probably more prevalent than is commonly appreciated, may prove difficult to detect by ordinary clinical methods. Much remains to be learned of the influence of diet on the maternal morbidity and mortality, on the incidence of abortion and prematurity and on the production of foetal deformities. Several large group experiments have been conducted in which special food supplements have been administered to the pregnant woman. In one group [664] receiving yeast extract or marmite, a reduction of neonatal and stillbirth mortality was noted. Ebbs *et al.* [665] found smaller neonatal mortality and morbidity figures among the infants of women on satisfactory diets, as compared with those of more poorly fed mothers. They considered that pregnancy and labour were more easily borne and that the mother's health in the puerperium was better when there was an improvement in the diet. The work in Britain inaugurated by the People's League of Health [666] revealed a decreased incidence of toxaemias of pregnancy, a diminution in the number of cases of prematurity, and a somewhat increased birth-weight, all apparently attributable to better feeding. The interpretations of such investigations has not escaped criticisms and Sinclair [667] questions the method of analysis of the data, suggesting that more accurate scientific studies are necessary Leverton and McMillan [668] found that women, receiving a 5 oz. serving of meat daily in addition to their self-chosen diet during the period from four months before delivery until three months after delivery, had higher haemoglobin values, less oedema and better success with lactation than women who received a supplement of vitamin-B complex, or women who received no such supplement. During the six to seven months preceding the liberation of North-western Holland in May 1945 severe generalized undernutrition was marked in urban areas; during this period Smith [614] noted that about 50 per cent of the urban women became amenorrhoeic and presumably infertile, and that the birth-weight fluctuated in a manner which suggested that foetal weight gain was probably related to the maternal diet of the last half or last trimester of pregnancy. Smith was unable to ascertain the incidence of abortion, but in hospital practice stillbirths showed no rate of increase, nor was the neonatal mortality affected Williams and Fralin [669] could ascertain no

correlation between deficiencies of vitamins A, B_1, C or of protein with toxaemias of pregnancy or with the efficiency of lactation.

Since the foetus derives its tissue substance from the mother, former latent maternal deficiency states may become overt during pregnancy should the diet be below or near the minimal level The frequency of gastro-intestinal upset during pregnancy is a common predisposing factor to malnutrition as are the curiosities of appetite which may appear during gestation. The strain of labour, the effects of anaesthesia and of blood loss and subsequently of lactation add to the tendency to undernutrition as do the increased physiological requirements of the mother during pregnancy. The National Research Council of the United States (1948) recommend the following allowances of vitamins for the pregnant and the lactating woman: –

	Calories	Vitamin A I.U	Thiamine Mg	Riboflavin Mg	Niacin (Nicotinic acid) Mg.	Ascorbic acid Mg	Vitamin D I.U.
Pregnancy (latter half)	2,400	6,000	1·5	2·5	15	100	400
Lactation	3,000	8,000	1·5	3·0	15	150	400

Vitamin A

Vitamin-A deficiency in the female may be reflected in the presence of an abnormal number of cornified epithelial cells in the vaginal smear examination; the detection of this abnormality has been suggested as a measure for the recognition of avitaminosis A. In the rat, resorption of the foetus may occur in the early part of pregnancy when vitamin-A inadequacy exists [670]. Should foetal resorption not occur there is frequently impairment of the foetal growth or death in late pregnancy, and gestation is often prolonged [671] Death not uncommonly occurs shortly after delivery. The development of foetal abnormalities in the young of vitamin-A-deficient rats is referred to on p 168

Swift [672] considered that leukoplakia, kraurosis, pruritus and atrophic vaginitis are due to lack of vitamin-A absorption occasioned by low or absent gastric hydrochloric acid. He obtained good results from the oral administration of dilute hydrochloric acid, and advised the use of vitamin A. Hyams and Bloom [673] hold the view that leukoplakia is of metabolic origin due to a failure of utilization and/or absorption of vitamin A. They claim that uncomplicated cases of minimal leukoplakia can be cured with adequate doses of vitamin A and dilute hydrochloric acid.

According to Bougher [674] an ointment containing vitamins

A and D is curative for fissured nipples and he states that local application offers an excellent prophylaxis against puerperal mastitis.

The People's League of Health, in its survey of the nutrition of expectant and nursing mothers, found a deficiency of vitamin A to be the most common of the vitamin-deficiency states. Dieckman *et al.* [675] observed no alteration of the clinical course of pregnancy and labour or of the birth-weights of the babies born of mothers receiving supplements of vitamins A and D, or of either vitamin alone, as compared with a series whose diet was unsupplemented. Lund [676] observed that the fall of the blood-plasma level of vitamin A in the later part of pregnancy was influenced by the amount of vitamin A in the diet and that the plasma-vitamin-A values in general reflected the dietary consumption of the vitamin. The time of appearance of the decreased concentration depended in part at least on the vitamin intake. Within twelve to twenty-four hours after parturition there is an elevation of the plasma-vitamin A, the cause of which is still undetermined; once elevated, vitamin-A values are readily maintained during lactation, which, Lund considers, affords evidence against any greater vitamin-A requirements during lactation. Vilter and his associates [677] state that there is no clinical evidence that the course of pregnancy or the condition of the foetus are embarrassed by deficiency of vitamin A. Lund and Kimble [678] discovered decreased puerperal morbidity and reduced incidence of the complications of pregnancy, excluding toxaemia, in those women whose plasma levels of vitamin A remained near normal. Lund recommends the addition of 5,000 units of vitamin A during the second trimester, and 10,000 units during the third trimester, for the maintenance of the best possible plasma levels. Hirst and Shoemaker [679] could ascertain no significant obstetric complications in women presenting vitamin-A-deficiency states, whereas Green *et al.* [680] found that only 1·1 per cent of those receiving large supplements of vitamin A in the last month of pregnancy developed puerperal infection as compared with an incidence of 4·7 per cent in a control group. Byrn and Eastman [681] found no correlation between the plasma-vitamin-A levels and the occurrence of puerperal sepsis, abortion, premature labour, toxaemia and post-partum haemorrhage.

Vitamin B_1 and the Vitamin-B Complex

Deficiency of these vitamins in animals produces disturbance of the normal oestrus cycle and total deprivation may result in abortion or malformed young.

In certain parts of the world vitamin-B_1 deficiency in pregnant

women is of common occurrence. In the Western Hemisphere such conditions may also be encountered particularly if gastro-intestinal disturbances complicate pregnancy. That thiamine deficiency is prevalent in America was revealed by the studies of Williams *et al.* [682] who found about one-third of their patients to be inadequate in their supplies of thiamine. The People's League of Health discovered that about half the women examined were not consuming a satisfactory amount of the vitamin. Ebbs *et al.* [683] noted a relief of many of the trivial complaints and improvement in the mental outlook of pregnant women who received supplements of thiamine.

The use of thiamine has been advocated in the treatment of the vomiting and of toxaemias of pregnancy. As examples of the former are the reports of Epstein [684] who obtained success in 22 out of 25 cases of intractable vomiting by the intramuscular injection of vitamin B_1 and liver extract, and of Acosta [685] who recorded good results in 59 out of 60 women with severe vomiting following the intravenous injection of vitamin B_1, two doses usually sufficing. Considerable work has been performed on the value of thiamine therapy in the toxaemias of pregnancy and conflicting results have been presented. Nixon *et al.* [686] discovered that patients suffering from eclampsia excrete significantly less vitamin B_1 in the urine than do those in normal pregnancy; also the concentration of thiamine in the placenta is low. King and Ride [687] considered that the factor responsible for the considerable increase in toxaemias of pregnancy among the women of Hong Kong in the years 1939, 1940 and 1941, was the increased incidence of beriberi at that time. Browne [688] administered 3 mg. of vitamin B_1 daily to the end of pregnancy to 100 women who were not more than 20 weeks pregnant; he observed no beneficial effects in the prevention of pre-eclamptic toxaemia Kapeller-Adler and Cartwright [689] concluded that the therapeutic use of vitamin B_1 in pregnancy should be discouraged. It is important to realize that a vitamin-B_1 deficiency may be occasioned by a toxaemia of pregnancy and not necessarily participate in the aetiology, although influencing the clinical picture.

Favourable results have been recorded from the treatment of nausea and vomiting with pyridoxine [690, 691, 692]. The vitamin has been given by the oral, intramuscular and intravenous routes. Silbernagel and Burt obtained relief in 38 out of 40 cases treated with intravenous injection of pyridoxine, improvement occurring in six to twenty-four hours after the initial injection; the duration of the improvement was variable. On the other hand Hesseltine [693] reported failure from the use of pyridoxine in this condition. Pyridoxine has also been given to cases of chorea gravidarum. Rabin and Dulk [694] and Dutra [695] observed a favourable response to this mode of therapy.

Brzezinski *et al.* [696] divided a series of 326 pregnant women into four groups according to the amount of riboflavin present in the urine. There was no significant difference between any of the groups in the incidence of toxaemia of pregnancy, or of haemorrhage or infectious complications during pregnancy, labour or the post-partum period. A significant relationship was found during the second half of pregnancy between low riboflavin excretion in the urine and vomiting, prematurity, antenatal death of the foetus and the efficiency of lactation. Riboflavin deficiency in the mother had no harmful influence on the birth-weight of infants or on their further development.

Vitamin C

The plasma ascorbic acid level shows a slight fall towards the end of pregnancy and during and after labour an even lower level is reached [697]. Lund found that in general the dietary intake was reflected in the plasma values. The mean value for patients on an adequate diet was 0·95 mg. per 100 c.c. which fell to an average of 0·18 mg. per 100 c.c. in patients subsisting on poor diets; of the greatest influence on the dietary intake of the vitamin was the season of the year. In the investigation by the People's League of Health, vitamin-C shortage was found in about half the women examined, but the deficiency was not nearly so great as had been anticipated. The vitamin-C consumption should be given particular attention in the last weeks of pregnancy, during lactation and in decreased intake or absorption due to vomiting or other disturbance. Although the gingivitis of pregnancy may develop on the basis of a vitamin-C deficiency, the hormonal influences during pregnancy in this association have been stressed by Sinclair [698]. The usual form of hyperplasia of the gums is unaffected by vitamin-C therapy. The incidence of mastitis in a group of pregnant women, receiving a daily supplement of 50 mg. of vitamin C for nine months beginning in the sixth month of pregnancy, was compared with a control group who received no additional ascorbic acid to the dietary sources; in both groups the incidence of mastitis was high and unaffected by the increased vitamin-C intake [699]. No correlation was found between the occurrence of sore nipples in the nursing mother and the capillary resistance nor could the condition be ascribed to a vitamin-C-deficiency state [700].

Javert and Stander [701] consider that vitamins C and K may be important factors in the early growth of the embryo and in some examples of threatened abortions. They also make the suggestion that certain cases of ante-partum haemorrhage may arise from a deficiency of these substances, individually or together.

Vitamin E

Conflicting reports exist on the vitamin-E concentration of the blood in pregnant women. Varangot [702] found the level higher in pregnant than in non-pregnant women and higher also in the first trimester than in the third. Straumfjord and Quaife [703], on the other hand, noted that the plasma-vitamin-E levels tended to rise with the progress of pregnancy, being 65 per cent higher at term than in non-pregnant women. The concentration of vitamin E in the blood of the umbilical cord is much lower than that of the maternal venous blood, and there does not appear to be any sex difference in the values in newborn infants. For men and non-pregnant women, Harris *et al.* [704] determined an average blood level of vitamin E of 1·04 mg per cent.

Lund considers that the widespread distribution of vitamin E in foodstuffs renders a deficiency of this nutrient unlikely Vitamin-E therapy for sterility in woman has proved a failure.

Shute [705] advanced the hypothesis that a deficiency of vitamin E in the maternal blood allows oestrogenic factors to gain a dominant rôle and so interfere with uterine implantation. Vitamin E has been employed extensively in the treatment of threatened and of repeated abortion. Good results have been reported in the latter by Currie [706] and Watson [707] among others, but considerably more work is necessary before the prophylactic value of vitamin-E administration in recurrent abortion can be assessed Shute [708] found that a large percentáge of threatened miscarriages was averted by the administration of vitamin E Silbernagel and Burt [709] recommend its inclusion in the therapeusis of threatened abortion, and King [710] also strongly advises the use of vitamin E, preferably in association with vitamins C and K Shute [711] recommends also the use of wheat-germ oil in the treatment of abruptio placentae and considers that the dose required increases as pregnancy proceeds and that sufficient should be administered to control the symptoms in the individual case.

Congenital abnormalities would not appear to be prevented by the use of vitamin E Shute [712] reported two anomalous foetuses in 29 pregnancies during which the mother had been treated with wheat-germ oil Senile vaginitis was stated by Shute [713] to respond to vitamin-E therapy. Good effects were reported from the use of vitamin E in women with non-eclamptic late toxaemias of pregnancy [714].

Vitamin D and vitamin K are discussed under other sections (osteomalacia and vitamins in relation to disorders of infancy and childhood).

CHAPTER EIGHTEEN

THE VITAMINS AND THE ORAL STRUCTURES

The Mouth

MANY VITAMIN-DEFICIENCY states induce oral lesions, hence examination of the mouth offers a most valuable index of the existence of certain dietary inadequacies. The tongue may also be examined by such methods as the use of smoked paper to make tongue prints [715], by biomicroscopy [716] and by applying an inking solution to the tongue, which is then pressed against suitable printing paper [717].

Vitamin A

As with other mucous membranes, vitamin-A deficiency may be associated with hyperkeratotic changes in the oral mucosa, and keratinization and hyperplasia of the gums may appear. These changes are not among the common manifestations of avitaminosis A in man, but have been produced in the experimental animal; the oral abnormalities predispose to bacterial invasion, and, in a high percentage of rats, abscesses developed in the mouth [718]. Structural alterations in the salivary glands may, in the laboratory animal, be followed by diminution of the flow of saliva [719]. Adult human vitamin-A nutritional status is but rarely reflected by changes in the oral cavity, although suggestions have been put forward that hyperkeratosis of the gums occasionally may be a manifestation of the deficiency. In this respect the possibility of a relationship with leukoplakia has been presented by Abels and his colleagues [720].

Vitamin B_1

Thiamine deficiency in man has been observed to result in an increased degree of sensitivity of the oral structures, so that minor procedures such as dental scaling and polishing may evoke considerable pain [721]. Lack of vitamin B_1 in the human subject as a rule produces no oral pathology, but an interesting finding was that of Weiserberger [722], who noted small, oral, herpetic vesicles in elderly people suffering from thiamine deficiency, and he obtained good response to vitamin B_1 therapy. Burket and Hickman [723] reported satisfactory results with thiamine therapy in some patients affected with herpes simplex and aphthous stomatitis.

Riboflavin

A characteristic clinical picture develops in the oral structures in the condition of ariboflavinosis. Sebrell and Butler [724, 725] first directed attention to the aetiology of the syndrome. Essentially cheilosis and a typical glossitis are the distinguishing features. The earliest change is a pallor of the lips. At the angles of the mouth, the buccal mucosa remaining unaffected. Soon, maceration of the area is superimposed, and superficial transverse fissuring develops; the latter is usually bilateral, extending from the angles of the mouth and is associated with little, if any, inflammatory reaction. The fissures extend in a somewhat downward direction, and become covered with a honey-coloured crust which can be wiped away, usually without the production of bleeding. As the duration of the ariboflavinosis advances, other portions of the lips may demonstrate an abnormal degree of redness at the lines of closure, and subsequently fissuring and cheilitis involve the lower lip, the upper lip usually remaining relatively unaffected. The lateral margins and tip of the tongue show the first signs of the lingual involvement. An abnormal redness becomes visible, and the surface is gradually smoothed out because of the progressing papillary atrophy. In contrast to the atrophic changes of the filiform papillae, the fungiform papillae are congested and enlarged, and their surfaces are flattened, so that they present a mushroom appearance, characteristic of this type of glossitis. The dorsum of the tongue is described as 'pebbly' or 'granular' Indentations of the teeth are visible on the lateral aspects of the tongue, and the atrophy of the filiform papillae extends to other areas as separate irregular patches which later become confluent; in the final stages disappearance of all the lingual papillae occurs and the lingual surface is smooth and glazed. The tongue then is diminished in size due to atrophic changes An important aspect of ariboflavinosis is the peculiar colour of the tongue which, in contrast to the fiery-red aspect of nicotinic-acid deficiency, assumes a purplish-red or magenta hue. Jones *et al.* [726] described raw, red areas with serpiginous outlines on the palate in 5 per cent of their cases of riboflavin deficiency, and in some instances the fissures at the angles of the mouth were seen to involve the mucosa of the cheeks Other features not coinciding with the description of Sebrell and Butler were also referred to by Jones and his co-workers The gums show no alterations. Among the subjective phenomena are excessive salivation, pain during the act of eating, a burning sensation in the mouth and soreness of the lips.

Claims that this oral syndrome is specific of riboflavin deficiency have not gone unchallenged. Riboflavin has failed to improve

patients with the characteristic tongue lesions. Machella and McDonald [727] obtained curative effects in some cases from pyridoxine or yeast therapy, although riboflavin was ineffective. A similar report was presented by Smith and Martin [728]. Nicotinic-acid therapy has produced healing of the angular cheilosis [729], as has pantothenic acid [730] in certain cases. Finnerud [731] reviews the subject of perleche, a maceration with transverse fissuring of the oral commissures; the condition may be of infectious origin – bacterial or mycotic, or it may result from hypochromic anaemia, sensitivity to lipstick and chewing gum, deficiency of riboflavin, nicotinic acid or pyridoxine, or from malocclusion due to ill-fitting dentures. He concludes that it should be regarded as a form of intertrigo of the labial commissures analogous to intertrigo elsewhere. Wintrobe [732] states that in chronic hypochromic anaemia the cheilosis of riboflavin deficiency may be present, and the lingual changes in this disorder and in the Plummer-Vinson syndrome are well recognized, although not necessarily due to a vitamin-deficiency state. Darby [733] reports 6 cases of angular fissures and superficial glossitis which accompanied a chronic iron deficiency of mild degree; certain of these cases responded to iron therapy alone, and others to similar treatment after prolonged intensive treatment with various vitamin-B preparations had previously been without effect. The importance of this observation is obvious, and Darby emphasizes that confusion of the condition with vitamin-B-deficiency states probably often arises, and that on occasion the response to iron and vitamin therapy is mistakenly attributed to the latter treatment. A reasonable conclusion at which one might arrive is that, while riboflavin deficiency does result in the characteristic lesions described, other aetiological agents may be instrumental in producing a similar picture. This does not invalidate the rôle of riboflavin in specific cases, but indicates the importance of examining for other manifestations of riboflavin deficiency, and for other possible causative factors. That the oral changes fail to respond to riboflavin therapy may, in some instances, be explained by the superimposition of an infective process; in the original observations of Sebrell and Butler, it was distinctly stated that no fungi were discovered in the oral lesions. The successful action of pyridoxine and other vitamins may in part at least be dependent on their ability to promote the utilization and absorption of riboflavin; it has been demonstrated that pyridoxine and pantothenic acid exert such an action [734].

Nicotinic Acid

Acute deficiency of nicotinic acid is associated with oral signs. The

tip and lateral margins of the tongue are first involved, where increased redness and papillary enlargement are in evidence. With advancement of the deficiency, the whole tongue becomes affected in similar fashion, so that it presents a fiery red colour, and, if the condition be allowed to progress still further, the lingual surface becomes atrophic, appearing as if denuded of epithelium. Other parts of the buccal cavity are simultaneously involved. Engorgement and swelling in the region of Stenson's duct appear, and these changes may also be visible in other parts of the mouth which, in established cases, is involved in its entirety. Foci of ulceration, covered with a greyish membrane in which there is an abundance of Vincent's organisms, may be found, sites particularly prone to this affection being the ventral aspect of the tongue, the lower lip and the gums. Indentations of the teeth may be pronounced in the margins of the swollen tongue and fissures may appear in the tongue. The lips often become congested and painful, and show cracks and shedding of epithelium. The symptoms associated with the stomatitis resemble those of ariboflavinosis. Chronic nicotinic-acid deficiency produces congestion and papillary atrophy at the margins and tip of the tongue. Areas of atrophy may affect other parts of the tongue at a later period. The response to nicotinic-acid therapy in the acute case is remarkable, and in a week or two the ulcerations may heal, no special treatment being required for the associated Vincent's infection. Prolonged treatment is necessary for restitution of the papillary atrophy, the duration varying according to the length of time the lesions have existed. In the chronic deficiency state, nicotinic acid effects a very gradual improvement, and its administration may have to be persisted with for even more than a year. Manson-Bahr [735] considers that there is little difference in the condition of the tongue as it occurs in sprue, pernicious anaemia, the nutritional anaemias, idiopathic steatorrhoea and pellagra, and that they are probably of common origin and not specific to the disease in question; nicotinic acid gives the best results in treatment and riboflavin is a valuable adjunct. A deficiency of the vitamin-B complex was discovered in the examination of eight patients with pernicious anaemia by Cayer and his colleagues [736].

Other Components of the Vitamin-B Complex

Knowledge is scanty of the position of other members of the vitamin-B complex in oral pathology. Sydenstricker *et al.* [737] described a geographical type of lesion in the tongue of subjects subsisting on a diet deficient in biotin which responded to small doses of the vitamin. Rosenblum and Jolliffe [738] refer to lingual changes similar to those of ariboflavinosis which cleared up only

with pyridoxine administration, and, in dogs, lesions of the oral cavity have been described which were attributed to deficiency of pantothenic acid [739].

Vitamin C

Vitamin-C deficiency promotes oral changes only after it has existed for long periods. Crandon *et al.* [740] observed evidence of an altered state of the mouth only after six months in human volunteers, existing on experimental diets inadequate in vitamin-C content. Then the gingivae were noted to be swollen and congested. In acute ascorbic-acid deficiency, vasodilatation of the small vessels is reflected in the hyperaemic, swollen appearance of the gums, the site of primary affection being the interdental papillae, whence it extends to involve the marginal gingivae and then the alveolar gingivae; the region of the lower incisor teeth generally manifests the earliest signs of the lesions. As the process advances, increasing 'bogginess' of the gums becomes evident, and bleeding, which previously followed minor traumata, may now ensue spontaneously. Pain is marked, salivation profuse, and eating is difficult. Food débris and products of secretion accumulate in gingival pockets, and the liability to local infection is increased. The epithelium of the gums may give way, and ulceration and sloughing areas make their appearance, so that eventually the gums may consist of a series of pockets of pus. Scorbutic gingival affection does not appear in the child until the teeth have erupted, nor in the adult if all the teeth are absent. Chronic ascorbic-acid deficiency is not accompanied by the pronounced vascular engorgement of the acute stages. The vessels show only minor degrees of dilatation and oedema, and this, rather than redness, characterizes the picture. The interdental papillae are first involved and become swollen but not hyperaemic. Separation of the gums from the teeth allows of the collection of pockets of material derived from the food and oral secretions. Injury, resulting from ordinary mastication, aggravates the condition. Infection is superimposed, with ulcerative and necrotic consequences on the gingivae, and perhaps the formation of alveolar abscesses. Halitosis is marked. The teeth become loose and may eventually fall out as a result of absorption of the alveolar bone. At any time the chronic ascorbic-acid-deficiency state may be complicated by an acute deficiency, the resulting oral lesions then representing a combination of the two processes. The pain occasioned by the ingestion of food leads to a lack of desire to eat, and accordingly the degree of deficiency may be further augmented. In considerable measure the gingival changes are influenced by the degree of dental hygiene adopted by the patient; poor dental

conditions, dental sepsis and malocclusion are mentioned as examples of local conditions which also bear on this aspect. Vitamin-C therapy effects a remarkably rapid improvement in the manifestations of the acute deficiency, and after a few days the gums may resume their normal appearance. Not so dramatic is the response of the chronic state, and here local treatment in addition to ascorbic-acid therapy will be essential for resolution.

The Vitamins in the Treatment of Diseases of the Mouth

The diagnosis of 'gingivitis' is commonly made, but there would appear to be much laxity in the interpretation of the criteria for its establishment. Many different aetiological factors are capable of producing gum changes, and the vitamins form only one group. Faulty oral hygiene, defective oral structures, habitual mouth breathing, heavy metals, and infection are among the causal factors. Objectively, the gums are inflamed and bleed readily with minor degrees of injury; the patient complains of pain and tenderness and bleeding of the gums. Coulson *et al* [741] concluded that nicotinic-acid deficiency played no part in the development of gingivitis of any type among the subjects they examined. The rôle of vitamin C has been disputed. Routine examination of recruits to the Royal Canadian Air Force revealed an incidence of lesions of the gums of 20 per cent; the histological appearances showed no resemblance to those of vitamin-C deficiency [742]. A diagnosis of a scorbutic gingivitis in the absence of other signs of ascorbic-acid deficiency is not warranted, but the possibility of a good therapeutic effect of vitamin C in gingivitis of other aetiology is not thereby excluded. Roff and Glazebrook [743] reported an incidence of gingivitis in British naval trainees four times as great in those consuming ordinary diets as in those also receiving supplements of vitamin C. Campbell and Cook [744] treated 14 patients with gingivitis with 300 mg of vitamin C daily, and on an average the gums became normal after approximately four days, although no simultaneous dental treatment was adopted. Stuhl [745] considered that the effects of local treatment in cases of gingivitis are improved if vitamin C is prescribed at the same time. An investigation conducted by Ungley and Horton [746] on naval personnel produced no evidence of a nicotinic acid or ascorbic acid deficiency state in those suffering from sore or bleeding gums. Administration of 500 mg of nicotinic acid resulted in no improvement; the amount of vitamin C consumed, as estimated from the dietaries, averaged 37 mg daily, and they concluded that deficiency of vitamin C was not a primary cause of the gingival changes in their series. Macdonald [747] also found the diet to be adequate in

vitamins in naval ratings affected with bleeding *gums or gingivitis*. Bleeding gums in an examination of 2,962 personnel of the Royal Air Force occurred in 19·8 per cent; *no beneficial effects resulted* from ascorbic-acid therapy in such cases, nor in those with sponginess' of the gums [748].

In the Canadian series, already referred to, while vitamin C and other vitamins were without therapeutic effect, *it was observed* that the tendency to recurrence of the gingivitis was greater when the diet contained *only 10 mg. of ascorbic acid daily*, as against a dietary intake of 75 mg. daily; this would seem to demonstrate a *prophylactic action of vitamin C*. It is difficult to arrive at any very definite opinion as to the value of ascorbic acid in the therapy of *non-scorbutic gingivitis*, but it would appear that the prevailing view does not favour any therapeutic influence.

The similarity between Vincent's stomatitis (ulcero-membranous stomatitis) and the oral manifestations of *nicotinic-acid* deficiency *has led to the exhibition of this vitamin* in its treatment. King [749] advocated the administration of nicotinic acid in conjunction with dental treatment, hydrogen-peroxide mouth washes and the application of chromic acid; a dose of 50 mg. thrice daily for the first week and twice daily for a further seven to fourteen days was suggested. Infants and young children were reported to respond to nicotinic-acid therapy in a more satisfactory manner than to methods of local treatment. Johnson [750] states that in four years' experience with this mode of therapy he found that a week's treatment was usually sufficient to *promote a cure; he considers* that a dosage of 50 mg. of *nicotinic acid thrice daily for adults and* of 10 mg. thrice daily *for children (or more according to* age) is as effective as penicillin. *There are other reports in the literature* which credit nicotinic acid with a beneficial action in Vincent's infection of the mouth, but *it is difficult adequately to gauge the* status of the vitamin in this disorder in view of the records of contrary findings [746, 741, 751]. *It is not sufficient to exclude* a therapeutic basis for nicotinic acid on the grounds of an intake of the vitamin sufficient for normal daily *requirements; similarly* absence of evidence of a deficiency state does not exclude its beneficial action, since a pharmacological action may be produced as distinct from the purely nutritional function. Contradictory observations are also on record as to the value of vitamin C in oral Vincent's infection

Nicotinic acid has been successfully employed *in the treatment* of xerostomia [752]. The painful state of the tongue in pernicious anaemia usually *disappears with liver treatment*. Should it persist, it may indicate insufficient dosage or a coincidental vitamin-deficiency state *in the causation of the glossitis*; riboflavin or nico-

tinic acid administration may be necessary in the latter instance. Folic acid will usually alleviate the glossitis. Gingival hypertrophy is a well-recognized complication of the treatment of epilepsy with sodium diphenylhydantoinate. On the assumption that a vitamin-C deficiency might be the underlying aetiology the vitamin was advocated, but has not proved of value as a prophylactic or curative agent [753]. Oral carcinoma may be associated with the manifestations of vitamin-B-deficiency states in the mouth, and the combination of the two conditions has been not infrequently observed [754, 755].

The Teeth

Vitamin A. – Deficiency of vitamin A in animals is succeeded by striking dental changes. Enamel formation is imperfect, the normal orange pigment of the enamel is absent so that the tooth presents a paper-white appearance, the dentine structure is imperfect, lacking the normal tubular arrangement, and the pulp is invaded by the odontogenic epithelium; eruption is retarded and odontomes may be formed [756]. King [757] states that in animals vitamin-A deficiency exerts its maximum effects on the gum and alveolar bone during early life. Hyperplasia of the subgingival epithelium attaching the gum to the tooth structure develops, and the dimensions of the alveolar bone are increased. The growth of dentine of the permanent tooth roots is arrested, and a mass of cementum is deposited in its place. The retardation of dental eruption is associated with malalignment of the teeth. Vitamin A exerts a definite influence in the maintenance of growth and normal structure of [illegible]
deficiency states the [illegible]
the enamel organ [illegible]
vitamin is reduced to zero levels the enamel organ ceases to grow. In children under 6 years of age hypovitaminosis A may interfere with the developing tooth germ; after this age the crowns of all the teeth, with the exception of the third molars, are completed. According to Wolbach [758] vitamin-A deficiency during the formative period of the teeth outranks, in the human subject, all other vitamin deficiencies in importance. However, it would not appear from the literature that disturbances of dental development are of common occurrence. Boyle [759] records an example, but Bloch [760] was unable to find any dental changes in children suffering from xerophthalmia and blindness produced by vitamin-A deficiency. Sarnat and Schour [761] discovered no association between enamel hypoplasia and vitamin-A deficiency in a series of 60 patients. In the adult human subject vitamin-A nutrition does

not appear to influence the structure of the dental tissues. Hypervitaminosis A is without effect on the dental structure [762].

Dental Caries. – Dental caries is widespread and affects almost every adult and every child over 6 years of age [763]. Over 95 per cent of children of 10 years of age have one or more decayed permanent teeth; by the age of 18, on an average, 9 permanent teeth have become decayed and several have been removed. The calcified tissues of the teeth – enamel, dentine and cementum – are prone to two main disorders: hypoplasia or defective structure and dental caries. Hypoplasia develops in the antenatal period and the post-natal period before eruption has taken place [764]. Mellanby [765] in her experiments with puppies was able at will to produce perfect or imperfect teeth by variations in the diet during the period of tooth development. The fat-soluble vitamins were the chief determinants of healthy structure, especially vitamin D, the optimum action of which was effected in association with an adequate intake of calcium and phosphorus. A deficiency of vitamin D during pregnancy and lactation resulted in imperfect calcification of the deciduous teeth, and, in lesser degree, of the permanent dental structures of the animals. Mellanby examined the structure of the shed and extracted teeth of children, and found that the teeth of good structure showed a lesser incidence and degree of caries than did those of defective structure; such a relationship did not necessarily apply to the relatively few teeth affected with gross structural defect. The assumption was that hypoplasia predisposed to caries, and that vitamin D, administered to the mother during pregnancy or at a sufficiently early stage to the child, would prevent hypoplasia, and so caries. This conclusion has been criticized in the light of subsequent investigations. Supplements of calcium, with or without vitamin D, have failed to influence the onset of dental decay [766, 767]. The teeth of children born of osteomalacic mothers were examined by Day [768] and no deleterious effects were noted beyond marked enamel hypoplasia in some; the teeth were remarkably free of caries. Youmans *et al.* [769] could discover no relationship between extensive dental caries and calcium or vitamin D intake, and Schour and Massler [756] state that avitaminosis D does not always result in enamel hypoplasia; when such does occur it is probable that some other condition, such as infantile tetany, has been interposed. Fiel and Shaw [770] pointed out that, in Johannesburg where rickets is non-existent and where the actinic rays received from the sun are ten times as much as in England, a study of 600 children revealed caries in 500. This is in contrast to the findings of East and Kairer [771], who reported that the greater the amount of sunshine in an area, the lower was the rate of caries McBeath

[772] recorded equally favourable results when vitamin D, milk or cod-liver oil were administered, and Brodsky *et al.* [773] noted a significant decrease in the number of new cavities in experimental groups following a single massive dose of vitamins A and D. Allen [774] reported a definite association in school children between the quality of the tooth and the amount of caries present. It would seem that the position of vitamin D in respect to caries is not yet established, and that evidence of its function in this direction is of an indirect nature.

Conflicting results have also been obtained with regard to the influence of the general nutritional levels of a community on dental caries. Klein and Palmer [775] concluded that the economic status did not influence the incidence of caries, although the level of dental care increased with improvement in the economic circumstances. Shourie [776] arrived at a similar result in a study

communities, and the lowest in the poorest communities. Two large-scale surveys in London County Council schools of 5-year old children in 1943 and 1945 were conducted, and the results compared with analogous groups examined in 1929; a great improvement in the deciduous teeth and in their resistance to decay had occurred in the intervening period, and this was attributed to the improved feeding habits of the pregnant and lactating mothers and of the children [778]. In the opinion of Boyd [779] the diets which were most effective in preventing caries had a high content of milk, vegetables, fruits and eggs. Vitamin A and vitamin C bear no relationship to the development of caries [756]

Vitamin D – Vitamin-D deficiency in man and in animals leads to imperfect calcification of the dentine The enamel structure remains unaffected as a rule, and, although the experiments of Mellanby [765] suggested that hypoplasia was of frequent occurrence, other work [780] has tended to incriminate some complicating factor in association with the rachitic state, such as deficiency of calcium If the latter theory represents the correct interpretation, it would tend to throw further doubt on the influence of vitamin-D deficiency in the production of caries. The eruption of the temporary and permanent dentitions is retarded in hypovitaminosis D, and the deformities of the jaws, which may be present in rickets, may cause malocclusion Becks [781] noted disturbances of the cementum and dentine, and abnormal tooth formation in dogs, following the administration of toxic doses of vitamin D. While the adverse effect of hypervitaminosis D on the

dental structures has been demonstrated in animals, little information exists as to its influence on the human teeth; Zisker *et al.* [782] found no change in pulp stone formation in 8 patients receiving daily doses of about 300,000 I.U. of vitamin D for periods of from 103 to 231 days.

Vitamin C. – In vitamin-C deficiency states the attachment of the teeth to the gums is involved, the teeth become loose and may eventually fall out. Apart from these effects, animal studies have yielded evidence of a function of ascorbic acid in the normal development of the dental structures. In the absence of vitamin C there is faulty formation of the intercellular substance of the dentine, cartilage and jaw bones. The subject is reviewed by Burket [783]. The structure and function of the osteoblasts are deranged, and an osteoid tissue is produced instead of tubular dentine; engorgement and haemorrhage of the vessels of the pulp may occur. In severe cases the ameloblasts also suffer and may even disappear; as a consequence enamel defects ensue. The cement layer between the gum and dentine fails to develop in normal fashion, so that fixation of the tooth in the jaw is defective [784], and this is further aggravated by the osteoporosis and atrophy of the alveolar bone. Caution must be exerted in applying the results of animal experimentation to the effects of avitaminosis C on the human teeth. Wolbach [784] did not discover similar dental pathological changes in human scurvy. Congestion of the pulp, and alterations in the dentine and odontoblasts, were reported by Westin [785] in scorbutic states in the human adult. Lack of vitamin C in the human apparently may be evidenced by dental derangement, but this would appear to be relatively rare, if one excepts the defects of the attachment of the tooth to the jaw.

Other Aspects. – Hickman and Harris [786] observed that patients receiving tocopherols required much less frequent removal of tartar from their teeth.

The continued use of lemon juice may result in a dissolution of dental structure, and its prolonged consumption should be discouraged [787]. Large doses of ascorbic acid have been reported to be of value in promoting the healing of tooth sockets following extraction [788]. Nicotinic acid exerts a haemostatic effect when applied locally [789]. An 0·6 per cent solution proved a satisfactory procedure in the arrest of haemorrhage from a tooth socket, and 100 mg of nicotinic acid by oral administration thrice daily was also very valuable. A patient, who on two previous occasions had required hospitalization for blood transfusions following dental extractions, was given 200 mg nicotinic acid daily for two days prior to extraction, and the sockets were plugged with packing containing equal parts of nicotinic acid and sulphathiazole; promp

clot formation resulted and there was no untoward post-operative bleeding [783]. Repeated extractions were performed at subsequent dates, with the same mode of therapy, and haemorrhage did again not occur as a complicating factor, as it had done on former occasions. Another interesting aspect of the vitamin-B complex is the low incidence of dental caries reported in pellagrins; 41 patients with clinical manifestations of pellagra averaged 2·1 cavities, while 10 patients without any clinical evidence of a vitamin-deficiency state averaged 6·1 cavities [790].

CHAPTER NINETEEN

THE VITAMINS IN DISEASES OF THE GASTRO-INTESTINAL TRACT

Vitamin A

FACTORS WHICH interfere with the absorption of fat also affect the absorption of vitamin A and its provitamins. Thus absorption may be poor in coeliac disease, sprue, cystic fibrosis of the pancreas, congenital obliteration of the bile ducts, intestinal obstruction, ulcerative colitis, dysentery, and in diarrhoeal conditions [791]. Short-circuiting operations may also diminish vitamin-A absorption from the gut; fistulous communications, especially gastro-colic fistula, may act in a similar manner, but after the abnormality has been corrected by surgery, absorption may return to normal. In a series of patients suffering from carcinoma of the gastro-intestinal tract, 86 per cent showed a diminution in the plasma level of vitamin A [792]. There is in such instances usually a satisfactory intake of the vitamin and no evidence of a decreased capacity of the liver to store the vitamin. Doses of from 50,000 to 150,000 I.U. administered parenterally were ineffective in raising the plasma levels of vitamin A in gastro-intestinal carcinoma [793]. Yeast, pancreatic extracts and choline proved effective in raising the plasma-vitamin-A concentration, suggesting a possible relationship of vitamin A and choline, the latter being essential for normal metabolism of vitamin A.

Contradictory reports exist as to the action of vitamin A on the secretion of gastric hydrochloric acid Boller [794] treated cases of duodenal and gastric ulcer with vitamin A and claimed good results. A beneficial effect of vitamin-A administration in the healing of gastric ulcers was also reported by Seelig [795], but Douthwaite [796] from a study of this form of treatment in 12 cases of chronic gastric ulcer concluded that the use of vitamin A in this condition is not justified

While in man vitamin-A deficiency may result in diarrhoea, the latter state may in itself, if of long duration, be the cause of hypovitaminosis A Excessive loss of nutrients in the stools predisposes to the latter condition, and in chronic intestinal diseases acts in association with malabsorption. Vitamin-A absorption tests revealed, for example, that, in chronic ulcerative colitis, the plasma-vitamin-A levels did not rise as high as in control subjects following administration of the test dose [797]

As with all vitamins, the occurrence of vomiting, anorexia an

mal-functioning of the gastro-intestinal tract may lead to avitaminosis A consequent upon inadequate intake, imperfect absorption, increased excretion or a combination of these mechanisms.

Coeliac disease and other conditions which interfere with fat absorption are associated with low plasma-vitamin-A values [798]. A useful diagnostic test is the failure of such cases to exhibit an elevation of the plasma vitamin-A concentration following oral administration of the vitamin. The carotene content of the plasma is also markedly reduced, and in advanced stages of the disorders the plasma may be almost colourless.

Vitamin B

The Appetite and Vitamin B. – While anorexia and nausea are symptoms of thiamine deficiency, only in the presence of other signs of avitaminosis B_1 can their aetiology be considered due to lack of the vitamin Thiamine will counteract these symptoms when they are attributable to diminished body stores of the vitamin, but there is no justification for the indiscriminate use of thiamine in the treatment of anorexia.

An interesting investigation on the relationship of the effects of various vitamin deficiencies on the appetite of rats for protein, carbohydrate and fats was conducted by Richter and his co-workers [799]. Rats on a diet deficient in the vitamin-B complex showed an aversion for carbohydrate and protein, and a craving for fat The appetite returned to normal after the administration of yeast, but with the addition of riboflavin, nicotinic acid or pyridoxine alone the appetite for protein was minimal. A combination of thiamine and riboflavin increased the appetite for protein and this was further enhanced by the successive additions of pyridoxine and nicotinic acid A combination of all four did not raise the appetite even approximately to the level attained following administration of the yeast supplement [800, 801]. Normal human subjects exhibited a marked correlation between their intakes of protein and thiamine [802]. The aversion of thiamine-deficient rats to carbohydrate can be explained by the disturbance of carbohydrate metabolism in avitaminosis B_1, and the aversion to protein on a similar basis, since so many of the amino-acids are convertible to glucose The explanation of the other effects is not as yet clear, but the influence of the dietary constituents on the intestinal flora, and thus on vitamin synthesis, is now beginning to be appreciated

Gastro-intestinal Motility – Diminished gastro-intestinal tone occurs in vitamin-B_1-deficient animals Thiamine-deficient diets produced varying grades of atonicity and dilatation of the entire gastro-

disease, tropical sprue, non-tropical sprue, Gee-Thaisen disease and Gee-Herter disease are identical conditions. Steatorrhoea may also arise from defective fat absorption occasioned by mechanical obstruction of the flow of chyle; tuberculosis, lymphosarcoma or Hodgkin's disease may account for the pathological changes in the mesenteric lymph nodes [817]. A sprue-like syndrome may develop in chronic and relapsing dysentery [818] and in intestinal giardiasis, but the latter as well as other infestations are not infrequent complications of tropical sprue. Gastro-colic or entero-colic fistula of malignant or non-malignant origin may present a similar picture.

Aetiology. – Various theories have been advanced to explain the origin of sprue. Stannus [819] considers that in sprue neutral fat is absorbed normally, but that fatty acids, glycerol, cholesterol and glucose are poorly absorbed. The defective absorption of these substances is due, he states, to a failure of phosphorylation, which is an essential process for their absorption by the intestinal mucosa. According to Black *et al.* [820] the defect in fat absorption in sprue is partial, for even in moderately severe cases 60 to 80 per cent of the ingested fat is absorbed. With this degree of steatorrhoea, absorption of glucose and other substances is satisfactory, but as the disease progresses the absorption defect becomes more generalized, and glucose, iron, sodium, chloride and nitrogen absorption is impaired The fault is not in intestinal secretion of fat, in diminished motility of the villi, nor in reduction of absorptive space, but in the failure of an enzyme system It would now appear that folic acid may be the missing factor, and its supply allows of normal functioning of the enzymatic activities.

Clinical Features. – The stools are described as bulky, pale, frothy and foul smelling, but there is much variability in the appearance of the stools, which may be liquid and brown, well pigmented and formed, or of 'dirty dishwater' nature. Microscopic examination reveals excessive amounts of split fat and soaps and, in uncomplicated cases, no blood or pus. During periods of remission a more or less normal aspect of the faeces is found. Dyspepsia, diarrhoea, flatulence, and abdominal pain are frequent. Loss of weight may be pronounced.

The other prominent features of sprue are referable to defective absorption of various essential factors. Leishman [821] found tha[t] almost all the patients had oral lesions. Glossitis, angular cheilosi[s] ulceration and fissuring of the tongue may occur. The skin chang[es] include follicular hyperkeratosis and pellagrous lesions. Rick[ets] and tetany may be manifestations, and hypocalcaemia a[nd] osteoporosis are encountered. A macrocytic, hyperchro[mic] anaemia is common, but normocytic, normochromic anae[mia] or microcytic, hypochromic anaemia may result. Eleva[...]

of the prothrombin time is a frequent finding. The above features are expressions of the defective absorption of the various essential nutrients concerned. The plasma-vitamin-A and carotene levels are reduced, and vitamin-A tolerance tests yield but little increase in the plasma concentration. Malabsorption of vitamin D and calcium account for the bone changes, and the hypoprothrombinaemia is due to faulty vitamin-K absorption. Deficiency of vitamin B, including folic acid, explains many of the other clinical manifestations. Low plasma tocopherol values are reported, and there is a diminished rise in the plasma tocopherol level following the oral administration of 600 mg. of tocopherols [822]. X-ray studies of the intestinal tract reveal the 'deficiency pattern'; in advanced cases hypomotility and dilatation, most marked in the jejunum, obliteration of the mucosal folds, excessive amounts of intestinal gas and collection of the barium in clumps separated from one another throughout the small intestine ('puddling') are evident [823].

Other features of sprue are absence or diminution of the gastric hydrochloric acid, a flat glucose tolerance curve, and diminished levels of blood calcium, phosphorus and ascorbic acid.

Treatment. – Prior to the isolation of folic acid, the accepted treatment was a diet low in fat and high in protein. Vitamins were prescribed to correct the existing deficiencies, and yeast was a valuable therapeutic agent Liver extract afforded a satisfactory measure in the treatment of the disorder. Tetany is treated along the usual lines and iron is prescribed for an iron-deficiency state.

Folic acid now provides a simple and usually adequate method for the control of the sprue syndrome The resulting improvement is reflected in the intestinal and haemopoietic systems, in the oral lesions and in the general health [823, 824, 825, 826]. The number of stools per day decreases, and the form of the stool changes, so that the motion assumes a normal appearance Radiological examination of the intestinal tract demonstrates that following folic-acid therapy the irritability of the small intestines reverts to the normal picture. The haematological response is evident in the peripheral blood and in the bone-marrow pattern Reticulocytosis, and an increase of the haemoglobin and of all the cellular elements of the blood takes place, and the bone-marrow returns to normal. The glossitis may disappear in a few days, and the patient soon gains weight and strength Oral glucose tolerance tests made before and after folic-acid therapy reveal evidence of improved absorption [827] No correlation was discovered between improvement or otherwise of fat-balance tests and improvement in the clinical or haematological condition [828]. The presence of pathogen…

See Addendum to this page at end of book.

Dosage is discussed by Suarez, Spires and Suarez [830]. They concluded that the adequate maintenance dose of synthetic folic acid is between 2·5 and 5 mg. daily in the majority of cases. The dose is influenced by the nature of the diet. Patients consuming a diet rich in animal protein and poor in carbohydrate and fat will require a smaller amount of the substance than those receiving a diet low in animal protein and high in carbohydrate and fat. The administration of folic acid in small daily doses produces a more pronounced therapeutic effect than single large doses.

Vitamin C

Achlorhydric patients usually show a low blood ascorbic acid value. Diminished intake occasioned by nausea, anorexia and vomiting may seriously lower the body stores of vitamin C. A case of purpura developing in anorexia nervosa was described by Aggeler *et al.* [831]. Diarrhoea and defective absorption in gastro-intestinal disease contribute to the development of hypovitaminosis C. Considerable loss of ascorbic acid occurs in the stools in conditions of diarrhoea, and vitamin C deficiency may arise in spite of a normal intake.

The prescription of special diets for patients suffering from peptic ulcer has resulted in the not infrequent production of a state of vitamin C deficiency. Vegetables and fruits are usually denied, while milk, eggs, bread and fish, which form the chief constituents of such diets, contain very little ascorbic acid. Low urinary vitamin-C excretion levels found in patients with peptic ulcers were due to a diminished dietary intake of the vitamin [832]. Warren *et al.* [833] estimated that the first week of the Sippy diet afforded only a daily intake of 5 mg. of ascorbic acid, while, in the fourth week, this diet allowed about 15 mg. of vitamin C daily. It is obvious that vitamin-C supplements should be added to the specialised diet of those affected with peptic ulcer, and this is further emphasized by the rôle of the vitamin in the healing of wounds [834]. The lowest levels of ascorbic acid were observed in haematemesis and melaena; in view of the importance of vitamin C in the integrity of the capillaries this deficiency may perpetuate and increase the bleeding. Pyloric stenosis is frequently associated with avitaminosis C, and restoration of the tissue reserves is particularly indicated prior to operation. The necessity for ample body stores of vitamin C in peptic ulcer i evident, but it cannot be assumed that vitamin C will assist in th healing of an ulcer or in the cessation of haemorrhage if no deficienc of the vitamin exists. A good procedure is to saturate the bo rapidly with 500 to 700 mg. daily, and then continue with 50 m thrice daily. Frank scurvy has been described in cases on u supplemented peptic ulcer diets [835], but these are rare, and i

those cases without clinical evidence of a lowered vitamin-C status which are common. No interference with vitamin-C absorption was observed during the administration of alkalis [836].

Cincophen-produced peptic ulcers in dogs were prevented in 60 per cent of cases by the simultaneous administration of ascorbic acid or calciferol [837].

Vitamin K

Hypoprothrombinaemia may be found in infants suffering from pyloric stenosis or congenital obstruction of the alimentary canal. Inadequate intake and impaired biosynthesis may account for the low prothrombin levels, and it is essential to correct these prior to operation. Sulphonamide administration may affect intestinal biosynthesis. Hypoprothrombinaemia may occur in infants affected with chronic diarrhoea [838]. It is clear that a vitamin-K deficiency may attend a wide range of gastro-intestinal disorders in childhood, and be further accentuated by their treatment with sulphonamide preparations.

Similar conclusions apply to the adult. Neoplasms of the gastro-intestinal tract, the steatorrhoeas, pancreatic disease, chronic colitis, ulcerative colitis and chronic obstructive lesions may be mentioned as examples of the large group of conditions which predispose to lowered plasma prothrombin values and to haemorrhagic manifestations. Butt *et al.* [839] observed low prothrombin values in the plasma of patients with intestinal fistula (internal and external), chronic ulcerative colitis and intestinal obstruction The need for the correction of the prothrombin level is obvious, and is of especial importance in those disorders in which bleeding is one of the components of the clinical syndrome.

CHAPTER TWENTY

THE VITAMINS IN HEPATIC PHYSIOLOGY AND PATHOLOGY

Vitamin A in Hepatic Physiology and Pathology

CAROTENE IS converted to vitamin A in the liver through the agency of an enzyme, carotenase, and the liver is the chief site of storage of the vitamin in the body. The Kupffer cells are the last to lose their content of vitamin A and the first to be replenished; the vitamin is absorbed from the plasma by the Kupffer cells and passed on to the liver cells, which appear to represent the permanent depots [840]. Vitamin-A storage in the liver is increased if vitamin E be administered at the same time as the vitamin-A-containing foodstuff is fed; all three tocopherols are equally effective but too small or too large dosages of vitamin E show a less pronounced effect, and vitamin-E esters are almost inactive [841].

Damage to the liver may be reflected in abnormalities of metabolism of vitamin A, either through impairment of the ability of the organ to transform carotene to vitamin A, or through alteration in the capacity of the liver tissue to absorb or liberate the vitamin. Diseased liver cells take up vitamin A at a faster rate and liberate it more slowly than do normal cells, and accordingly vitamin A may be present in the damaged, but not the uninvolved, liver sites [842]. The vitamin is no longer available for immediate release because of the avidity of the pathological areas, so that the plasma-vitamin-A level falls, and a vitamin-A deficiency state may eventuate. A peculiar state of affairs is thus created; ample quantities may exist in the liver but, by virtue of disturbance of the release mechanism, the other tissues remain deficient in supplies of the vitamin. Mere lack of intake cannot explain this anomaly, since several months are required to effect a corresponding drop in the plasma-vitamin-A level in human subjects subsisting on a diet deficient in this factor. It must not be assumed that a low plasma level reflects the state of the hepatic stores, since in the individual case no relation is necessarily found between the two values; a low hepatic store may be associated with a high or low plasma concentration. If vitamin-A therapy is to be effective in the presence of liver disease it must be administered in large doses in order that the healthy cells may receive the vitamin after the diseased areas have been saturated.

The plasma concentration of vitamin A is lowered in acute hepatitis. In cirrhosis accompanied by jaundice zero levels may be found, and a similar finding was discovered in 66 per cent of cases of secondary hepatitis due to malignant obstructive jaundice;

occasional zero values were obtained in cirrhosis without jaundice and in incomplete biliary obstruction, but the plasma-vitamin-A figure was higher in cases of cirrhosis without jaundice than with jaundice, and higher in obstructive jaundice without than with hepatitis [843]. The liver concentration of vitamin A showed similar tendencies, but often there were marked differences in the plasma and hepatic concentrations; in general, chronic liver diseases, such as cirrhosis, were associated with pronounced reduction in the reserves of vitamin A [844], but acute hepatic disorders may be accompanied by little diminution in the hepatic stores [845]. The normal values for the vitamin A and carotene content of the liver were obtained by the examination of the organ in 19 cases of accidental death, the values for vitamin A showing a range from 70 to 461 I.U. per gram, and 2 to 5·3 micrograms for carotene; in 35 specimens of liver from human embryos and newborn infants the vitamin-A content ranged between 45 and 665 I.U. per gram, while carotene was absent in 19 cases, and in the remainder the content was 0 5 to 2 1 micrograms per gram [846]. Skurnik and his colleagues [846] refer to the results of others who noted low reserves in infants, and suggest that the embryonic reserves may be higher in the earlier than in the later stages of development. An interesting observation was made by Gillman *et al.* [847], who found that vitamin A, administered in large dosage to pellagrins, did not result in as great an increase in the reduced liver stores of the vitamin as did the administration of ventriculin

Occasional reports have appeared of the development of clinical manifestations of a vitamin-A-deficiency state, such as xerosis and xerophthalmia, in chronic liver disease, but these are of infrequent occurrence. On the basis of the dark adaptation test many investigators have concluded that the vitamin-A status is considerably altered in chronic hepatic dysfunction

As in febrile conditions, the low plasma-vitamin-A concentration at the height of acute hepatic diseases has been succeeded, in the event of recovery, by a rise in the plasma concentration to levels above the normal [848] Impairment of liver function probably explains the transitory reduction of the plasma-vitamin-A level, and the heightened blood levels are probably more attributable to liberation of the vitamin from the pathological sites where it was retained [849] than to improved intestinal absorption as suggested by Clausen *et al* [850]. That the latter factor does participate is suggested by the work of Harris and Moore [851], who demonstrated the excretion in the faeces of substantial amounts of vitamin A following administration of massive doses of the vitamin in the early stages of infective hepatitis; similar doses did not pro-

inositol, which is a lipotropic agent, and the hepatic disorder can be alleviated by the administration of inositol [858, 859]. Handler and Dann [860] considered that nicotinamide was deleterious to the liver, since it removed methyl groups from choline to form trigonelline. Absence of pyridoxine and pantothenic acid increase the requirement for choline and inositol, expecially the latter [852]. Peters and Van Slyke suggest that excessive doses of vitamin-B components, in the presence of inadequate dietary intake, may be followed by injurious effects on the liver.

Therapeutic Effects of Vitamin-B Complex in Liver Disease. – The application of the results of animal experiments to the hepatic diseases of man is still in the process of elucidation. The aetiology of cirrhosis remains problematical. In 30 per cent of cirrhotic patients examined at autopsy a history of alcoholism was absent [861]. Cirrhosis is prevalent among the natives of India, Java and Ceylon where alcohol cannot be incriminated in its causation. The present-day tendency is to correlate cirrhosis with a dietary deficiency, and this view is strengthened by the work of Gillman [862] who produced hepatic cirrhosis in rats by administering to them the ordinary diet of natives in the mines of South Africa, among whom cirrhosis and necrosis of the liver are of frequent occurrence. A diet low in protein and in the content of vitamin-B complex, including choline, is the usual one consumed by subjects addicted to alcohol [855], and this dietary inadequacy may be offered as an explanation of the cirrhosis in these subjects, rather than the action of alcohol *per se*. Himsworth and Glynn [854] present the hypothesis that massive hepatic necrosis fundamentally originates from nutritional defect, whether primary or conditioned by existing hepatic changes with circulatory disturbances in the liver. That human cirrhosis is preceded by fatty infiltration, as in the experimental dietary induced cirrhosis of animals, has been demonstrated by Gillman and Gillman [863], who followed the evolution of the malady from the stage of fatty infiltration. The favourable effect of high protein diets and supplements rich in vitamin-B complex in cirrhosis of the liver has been recorded [864, 865]. The results of treatment of liver disease in man by dietary agents are difficult to evaluate in respect of individual members of the vitamin-B complex, since a combination of several was usually included. Choline and vitamins, in association with a high-protein, high-carbohydrate and low-fat diet effected improvement in 7 out of 10 cases of cirrhosis of the liver [866]. A very good response followed treatment with a high protein diet and choline in patients with enlarged cirrhotic livers, whereas poor results were obtained when the liver was shrunken [867]. It was also claimed that patients with congestive cardiac failure improved with regard to

both the liver and myocardial efficiency. Beams [868] recorded good results in patients with cirrhosis and enlargement of the liver in 7 out of 8 cases, but no response in 12 without enlargement of the liver by treatment with a high-protein, low-fat diet, supplemented by yeast and a combination of choline and cystine. Improvement following the use of choline in the therapeusis of cirrhosis with vitamin supplements, a diet low in fat and rich in protein is reported by Broun and Meuther [869], Barker [870] and Wade [871]. The early stages of cirrhosis are associated with fatty infiltration and enlargement of the liver, and if treatment is to be beneficial it must be instituted at this stage and before marked cirrhosis with contraction of the hepatic size has ensued. Equivocal results have been obtained in the treatment of infective hepatitis, both with large dosage of combinations of vitamins and with choline [872, 873, 874]. Beattie [875] reported a beneficial action of choline on kidney failure associated with severe liver damage in man, and Barclay and Cooke [876] record a case of the hepatorenal syndrome where death was considered inevitable, but which recovered following treatment with intravenous choline and methionine. The latter authors emphasize that intravenous choline therapy may be attended by severe sweating, bronchial secretion and painful abdominal cramp, and advocate the use of atropine in the prevention of the bronchial secretion; a diffuse macular rash appeared in their patient on the third day of treatment with choline, but spontaneously cleared up within seventy-two hours of cessation of the treatment. The use of inositol in daily doses of 600 mg. was considered helpful in the treatment of cirrhosis [877].

The situation of the available evidence of dietetic factors in the treatment of liver disease in man is summed up by Witts [855], who states that it is as yet too early to assess their value in the better-nourished populations, and that advances in the therapy of infective hepatitis and allied virus infections will probably arise from bacteriological research rather than from nutritional investigations.

Vitamin B_1

Thiamine does not appear to occupy an important place in the preservation of normal hepatic function, although liver disease tends to be associated with a diminution in its excretion Occasionally evidence of a thiamine-deficiency state may accompany chronic disease of the liver.

The position of the B vitamins *in relation to oestrogen inactivation* by the liver is discussed in the section on Endocrinology.

with vitamin-K absorption from the intestine, and vitamin-K administration remedies this defect, but the impairment of prothrombin formation by the damaged liver cells prevents complete restoration of the prothrombin level in the blood. Temporary and recovering liver damage, such as occurs in toxic hepatitis, shows a gradual rise in the plasma prothrombin concentration following vitamin-K therapy, coincident with the evidence of clinical improvement; the vitamin is absorbed from the gut, but cannot be utilized to the full extent. The fourth type of reaction is that encountered in chronic and long-standing liver disease, as for example cirrhosis, in which the prothrombin level fluctuates at subnormal values above the threshold for haemorrhage, irrespective of vitamin-K therapy. Finally, there are those patients whose plasma prothrombin falls in spite of therapy, and remains below the level for haemorrhage; this group has severe and widespread liver damage, and the subjects are severely ill, presenting haemorrhagic manifestations, an instance of this form of response being found in acute yellow atrophy of the liver.

Vitamin K and Haemorrhage in Liver Disorders. – Haemorrhagic complications of diseases of the liver are not solely dependent on the prothrombin content of the blood. Morlock and Hall [887], in a series of 80 cases of cirrhosis, found definite thrombocytopenia in 17·5 per cent, and although a haemorrhagic tendency was evident in many of these cases, regardless of the blood-platelet count, it was relatively twice as common when thrombocytopenia was present; not all the cases of thrombocytopenia exhibited haemorrhages. Thrombocytopenia was of even greater incidence in a group of 50 cases of splenic anaemia with a correspondingly increased frequency of haemorrhages, and the authors concluded that the reduction of platelets in cirrhosis was not a fortuitous finding. Aggeler and Lucia [888] discovered that while hypoprothombinaemia was the most common defect in the haemostatic equilibrium in patients with diseases of the liver and biliary passages, an accompanying prolongation of the bleeding time and the coagulation time and poor clot retraction were more frequently encountered in those with abnormal bleeding than in those with no haemorrhagic manifestations; these abnormalities were usually corrected if the prothrombin time could be elevated to normal. A further feature which they noted was a lack of relationship between the reduced platelet count, the increased capillary fragility and, in some instances, the prolongation of the bleeding time and the level of the prothrombin concentration.

The adverse effect of operative procedures on patients with liver disorders is borne out by the not uncommon occurrence of haemorrhage, for the first time, several days after the operation.

A fall in the prothrombin level has been observed at this period [889], haemorrhage being most common between the first and fourth post-operative days. Infection and anaesthesia also exert a deleterious action in this respect. Operations on the biliary tract are especially liable to promote haemorrhage; Lord [890] showed that simple manipulation of the liver in anaesthetized dogs results in a reduction of the plasma prothrombin level. It must not be thought that the level of plasma prothrombin is an absolute guide to the development of haemorrhage, for there is considerable individual variation. Haemorrhage has been reported in patients with liver disease in the presence of normal prothrombin times [891] and, while Brinkhous *et al.* [892] have suggested that a prothrombin plasma level of 35 per cent is the critical level below which bleeding occurs, lower values have been discovered in the absence of haemorrhagic phenomena. It is evident that haemorrhage in liver diseases is of complex origin.

Biliary Fistula – When bile is allowed to escape from the body through a biliary fistula, there may develop an inadequacy of vitamin-K absorption from the intestine, and haemorrhages may ensue. Oral administration of bile may prove effective in rectifying this defect Vitamin-K supplements alone, if prescribed by the oral route, may fail to relieve the lowered plasma prothrombin concentration, but will do so when bile is also prescribed. Water-soluble preparations of the vitamin do not require bile for their absorption from the intestinal tract Parenteral vitamin-K therapy rapidly restores the prothrombin level of the blood to normal.

The Indications for Vitamin-K Therapy in Liver Disease. – The prothrombin level of the plasma is the best guide. Obstructive jaundice produces a hypoprothrombinaemia which is primarily due to defective absorption of vitamin K from the intestines. Bile salts orally administered will remedy the absorptive disturbance, and vitamin K given simultaneously by mouth will rapidly restore the depleted tissue concentrations of the vitamin. Should the obstruction have produced a marked degree of liver damage, the hepatic tissues may fail fully to utilize the absorbed vitamin K in the formation of prothrombin, and the hypoprothrombinaemia may not be completely rectified The importance of the possibility of a fall in the prothrombin value of the plasma to dangerous levels following operations on the liver and biliary system, even when the pre-operative value was normal, has been stressed. The loss of the vitamin in the blood and exudates of the operation, the requirements of the vitamin in the clot formation of the wounds, and the diminished dietary intake after operation, are among the factors tending to diminish the plasma prothrombin levels, so that vitamin-K administration may be indicated following surgery on

Nicotinic Acid

Dogs affected with black tongue occasionally develop a severe macrocytic anaemia, which is curable with nicotinic acid [901]; besides this form of anaemia, a normocytic, normochromic anaemia may appear, which also responds to nicotinic-acid therapy.

A proportion of the cases of pellagra in the human show anaemia. The incidence of the haematological affection varies in different parts of the world. Turner [902] reported that anaemia was an uncommon incident in endemic pellagrous areas in the United States; Salah [903] discovered no example in 118 pellagrins, whereas Spies and Chinn [904] observed that anaemia was not infrequently encountered in alcoholic pellagrins. Moore and his colleagues [905] investigated the macrocytic form of anaemia of pellagra. A pronounced deficient diet had been consumed for many years, and signs of peripheral neuritis, ariboflavinosis and nicotinic-acid deficiency were present in most. The patients were chiefly in the older age-group, and the condition was largely confined to the male sex. Oral changes, subjective and objective, and gastro-intestinal dysfunction, including diarrhoea (but not steatorrhoea), were frequently present. Examination of the blood and bone-marrow revealed changes identical with those of pernicious anaemia, but the two conditions could be distinguished by the presence of free hydrochloric acid usually found in the gastric juice of the pellagrous patients. These latter also showed a normal icteric index and generally a normal serum iron level, both being elevated in Addisonian pernicious anaemia. Moore *et al.* concluded that none of the B vitamins was effective in treatment, and that the anaemia was due to a prolonged deficiency of the extrinsic factor of Castle in the diet; impairment of intestinal absorption might participate in its causation. Spies and his collaborators [906] found folic acid to be effective in the treatment of the macrocytic anaemia of pellagra. Turner [902] stated that a hypochromic microcytic variety of anaemia was the usual form seen in endemic pellagra in the United States. Moore *et al.* [907] studied 32 patients with hypochromic anaemia in whom nicotinic-acid deficiency, multiple neuritis or ariboflavinosis were present. No tendency for hypochromic anaemia to develop specifically in any of these deficiency states existed. Iron alone was effective in treatment, and brewers' yeast had no demonstrable action in increasing the efficacy of iron medication. Ungley [908] found that hypochromic anaemia, as it occurred in adult human subjects, did not respond to yeast or wheat-germ preparations, irrespective of whether or not the diet had been grossly deficient. From the evidence available it may be concluded that in man nicotinic acid

is not concerned with erythropoiesis or haemoglobin formation. Jolliffe and Stern [909] have observed instances of glossitis in Addisonian pernicious anaemia which failed to respond to diet and refined liver extract, even when a satisfactory haematological reaction had occurred; treatment with nicotinic acid effected a slow improvement, so that within a year the tongue had resumed a normal appearance.

Riboflavin

Experiments in animals have revealed an association of riboflavin with blood formation. Wintrobe and his collaborators [910] maintained young pigs on a riboflavin-deficient diet, and in two instances an anaemia developed; the anaemia was of moderate normocytic variety and showed a gradual progression. György *et al.* [911] discovered that riboflavin administration produced an increase of haemoglobin above the basal level in standardized anaemic dogs. Spector *et al.* [912] described an [illegible]

carried out, Spector *et al.* noted that a severe anaemia ensued, even though the amounts removed were small, and that recovery from the anaemia did not take place unless riboflavin was administered; a normocytic, hypochromic anaemia was witnessed following slight bleeding when only small amounts of riboflavin were added to the diet, and the conclusion reached from these findings was that riboflavin is concerned in the control of the size of the newly-formed erythrocyte. Waisman [913] reported a severe anaemia in riboflavin-deficient monkeys.

Dogs fed a diet deficient in riboflavin developed myelin degeneration of the peripheral nerves and posterior columns of the spinal cord [914] Because of the similarity of these neurological changes to those of subacute combined degeneration of the cord, Meyer *et al.* [915] investigated the riboflavin excretion both before and after oral administration of 5 mg. of the vitamin in patients affected with this disorder, and could ascertain no difference from that of the normal state, showing that there is no impairment of riboflavin absorption in achlorhydric subjects

In spite of the above and other experimental findings of a connexion between riboflavin and haemopoiesis in animals, there appears to be no deleterious effect on the blood picture in man accruing from ariboflavinosis. Moore *et al.* [907] failed to discover any improvement from riboflavin administration in the anaemia associated with states of riboflavin deficiency in human subjects, and Sebrell and Butler [916] in their experimental production of

hyporiboflavinosis in human volunteers could ascertain no fall in the red or white cell counts, or in the concentration of haemoglobin.

Choline

Davis has performed a series of experiments in animals with regard to the effects of choline on the blood picture [917, 918]. Choline chloride was found to reduce the marked polycythaemia induced in rabbits by cobalt chloride; 100 mg. of choline chloride introduced daily by the stomach tube caused partial reduction in the red cell count. When dogs were given choline chloride for fifteen days or longer, an anaemia developed which Davis attributed to dilatation of the blood vessels due to the action of the choline thus providing an increased supply of oxygen to the bone-marrow. Davis and Gross [919] added a quarter of a pound of butter and 400 mg. of choline to the breakfasts of two human subjects, and there resulted a rapid reduction of the red cell count during the following thirty-six hours, succeeded by a subsequent reticulocytosis. The explanation offered was that the products of fat digestion which had escaped resynthesis to neutral fat during absorption probably caused destruction of the red cells, while choline by its vasodilating effect on the blood vessels of the bone-marrow acted as a weak 'brake' in preventing compensatory activity of the bone-marrow.

The anaemia which Davis produced in dogs resembled pernicious anaemia, and was cured by liver extracts. Watson and Castle [920] treated a patient suffering from macrocytic anaemia and cirrhosis of the liver with choline, and did not observe any intensification of the anaemia but, in fact, a progressive increase in the red cell count and haemoglobin concentration. This result is contrary to what might be expected from the experiments in animals, and equally so is the report of Moosnick *et al.* [921] of a case of progressive Addisonian pernicious anaemia successfully treated with intravenous choline chloride. An examination of a biopsy specimen of the liver of the patient of Moosnick and his co-workers showed a fatty metamorphosis, and it was suggested that this had interfered with utilization of the liver extract previously administered. That, in these two cases of a beneficial response from choline therapy, the improvement of the blood picture may have been produced indirectly by improvement of fat transportation and of the hepatic function, seems likely. Davis and Brown [922] found that choline chloride given either orally or intravenously in daily doses of as much as 10 grams only occasionally exerted slight haematopoietic effect in several cases of different types of megaloblastic anaemia. Cartwright and Wintrobe [923] gave choline chloride in doses of 10 mg. per kg. of body-weight thrice daily to

three men, and observed no effects on the haematological picture. Carpenter [924] obtained no reduction in the red cell count in patients suffering from polycythaemia vera following choline therapy.

Pyridoxine

Pyridoxine deficiency produces a microcytic hypochromic anaemia in dogs [925] and in pigs [926], and treatment with the vitamin restores the red cell count and haemoglobin level to normal. Haemolysis does not account for the origin of pyridoxine deficiency anaemia [927], but there is an elevation of the serum iron concentration, haemosiderosis of the organs and a hyperplasia of the bone-marrow. It would not appear that pyridoxine is concerned with erythrocyte or haemoglobin production in man. Kark *et al.* [928] obtained negative results from the use of pyridoxine in 4 cases of anaemia in pellagra, 1 case of hypochromic anaemia and 1 case of nutritional macrocytic anaemia.

Pyridoxine has been employed in the treatment of agranulocytosis. Cantor and Scott [929, 930] reported the effective nature of intravenous pyridoxine given as a 10 per cent solution in physiological saline in the therapy of leucopenia of toxic origin. Fishberg and Vorgimer [931] and Taylor [932] also record a satisfactory response to intravenous pyridoxine. Cantor and Scott administered 125 or 200 mg. of pyridoxine daily. Menten and Graff [933] treated 22 children and 1 adult, in whom granulopenia had developed following sulphonamide therapy, with a combination of pyridoxine and folic acid, and there followed a satisfactory response of the granulocyte count to this form of therapy. Leys [934] injected 200 mg. of pyridoxine intravenously to 5 normal individuals on three successive days, and did not observe that pyridoxine in the dosage used had any appreciable effect in increasing the neutrophil count.

Vitamin C

Aron [935] described a mild hypochromic anaemia in adult guinea-pigs during the development of scurvy; the anaemia was cured, sometimes with dramatic suddenness, by the administration of ascorbic acid. Sigal [936] observed a decrease of haemoglobin and diminution in the number of erythrocytes in the induced ascorbic-acid-deficiency state of guinea-pigs. A marked decrease in the level of the plasma iron was noted in scorbutic rats by Braganca and Saha [937], while *intravenous injection of ascorbic acid increased* the concentration of the serum iron [938]. The liver content

of iron was not significantly reduced in scorbutic rats, and the possibility of a function of vitamin C in the transport of iron was suggested.

Conflicting views exist on the relationship of vitamin C to blood formation in man. Mettier *et al.* [939] attributed a specific erythropoietic action to ascorbic acid. Two cases of scurvy with anaemia were reported by Dunlop and Scarborough [940] to yield to supplementation of the diet with 60 mg. of vitamin C daily. According to Wade and his co-workers [941] it is unnecessary in scurvy to resort to iron or liver therapy until the haematological response to ascorbic acid has been observed. An investigation of the bone-marrow in 3 cases of scurvy by Israels [942] revealed evidence of diminished erythropoiesis in 2; following treatment with ascorbic acid the bone-marrow showed increased erythropoiesis, and the anaemia quickly responded without any other anti-anaemic treatment. Israels concluded that ascorbic-acid deficiency produces a depression of erythropoiesis rather than a failure of maturation at any particular stage. Parsons and Hawksley [943] considered that normal haematopoiesis does not occur in the absence of vitamin C.

While these and other reports are in favour of a specific function of vitamin C in blood formation, there is considerable evidence which does not concur with such a conclusion. Hess [944] observed that anaemia was not a constant concomitant of infantile scurvy, and indeed that polycythaemia was present in some scorbutic infants. The anaemia associated with scurvy does not necessarily parallel the severity of the deficiency state, and in general, adults appear to be more susceptible than those of a younger age-group Crandon *et al.* [945] could demonstrate no anaemia in the human subject submitted to an experimentally induced vitamin-C deficiency. The opinion of Abt and Farmer [946] was that when anaemia accompanies avitaminosis C, it is probably due to a generally deficient diet from which essential components other than ascorbic acid are lacking. Low colour-index anaemia in children, associated with border-line ascorbic acid status, responded as well to iron therapy alone as it did when a daily supplement of 100 mg. of ascorbic acid was also given [947]. Lin *et al.* [948] noted a frequent association of anaemia with conditions of vitamin-C deficiency, and from the results of their therapeutic measures concluded that the anaemia did not originate from lack of vitamin C *per se*, but from a concomitant iron deficiency.

These conflicting views make any decision on the subject difficult. Vilter and his associates [949, 950] reported a series of cases of anaemia in scurvy, the blood condition being rectified by vitamin C. They point out that a severe vitamin-C depletion may

not be attended with anaemia until additional deficiency of some other factor essential for haematopoiesis occurs. After anaemia has developed, deficiency of the latter factor, they state, may not be serious enough to prevent a remission with vitamin-C therapy. A deficiency diet in man is deficient in many substances and, depending on the nature of these other nutritional factors which are lacking, a varied therapeutic response will occur to vitamin C in patients with scurvy. They consider that the concept of a multiple deficiency state, with many factors besides avitaminosis C adversely affecting the bone-marrow, would offer a satisfactory explanation of the many conflicting reports on the subject of scorbutic anaemia.

The blood picture in the anaemia accompanying ascorbic-acid deficiency is very variable. McMillan and Inglis [951], in a series of 40 patients, found macrocytic anaemia in 2, normocytic anaemia in 18, simple microcytic anaemia in 14 and microcytic hypochromic anaemia in 6. Vilter and Woolford [949] found the red cell counts to vary from 1·74 to 3 million per c.mm. and the haemoglobin from 5·8 to 10·5 grams per 100 c.c. in a group of anaemic scorbutic subjects; the cells were normocytic or moderately macrocytic hyperchromic, and the bone-marrow picture varied considerably. Gottlieb [952] reported 4 cases of severe adult scurvy associated with a high colour-index anaemia; 1 died but the others responded to vitamin-C therapy.

In a study of the blood levels of the vitamins in Addisonian pernicious anaemia, Cayer *et al.* [953] found no significant alteration of the vitamin-A or vitamin-C concentration, although the vitamin-B values were low; while they were unable to show any correlation between the degree of anaemia and the vitamin levels, they suggested the use of the B complex as adjuvant therapy in pernicious anaemia. Low plasma-ascorbic-acid values were reported in pernicious anaemia by Alt and his collaborators [954]. Dyke *et al.* [955] observed 3 cases of pernicious anaemia which improved only when vitamin C was administered in addition to the liver therapy. A case of scurvy is reported by Jennings and Glazebrook [956] in which the blood picture was similar to that of pernicious anaemia.

Vitamin C has proved a valuable agent in the treatment of methaemoglobinaemia. Lian *et al* [957] suggested this mode of therapy, and Keise [958] demonstrated the reduction of methaemoglobin *in vitro* by ascorbic acid. Deeny and his collaborators [959] employed vitamin C and sodium bicarbonate (since the latter raises the renal threshold for the vitamin, thereby reducing its excretion in the urine) in two cases of familial idiopathic methaemoglobinaemia; daily oral administration was followed in a few weeks by a return of the skin colour to normal, which had been maintained

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in both cases for one year – to the date of publication. Subsequentl reporting on these same cases Barcroft *et al.* [960] observed tha continued treatment with daily doses of ascorbic acid of 200 to 30 mg. had kept the methaemoglobin at low levels. Vitamin-C therapy was followed by a rapid decrease in the concentration o methaemoglobin in two patients, in one of whom the conditio was due to nitrites and in the other the cause was undetermined 500 mg. of ascorbic acid was given intravenously to one, and a noticeable diminution in the degree of cyanosis was obvious withi four hours [961].

Barron and Barron [962] reported on the reduction of the ery throcyte count which succeeded the daily injection of vitamin C in rabbits affected with cobalt polycythaemia. While vitamin C alone produced no fall in the red cell count in two cases of human polycythaemia, when combined with sodium bicarbonate norma figures of the erythrocyte concentration were attained [963]. Vitamin C was found to be ineffective in the treatment of poly cythaemia by Kandel and Le Roy [964].

The increased white cell count of leukaemic subjects is associated with an increase in the blood content of vitamin C. Extremely high values were observed by Stephens and Hawley [965]. There appears to be a difference in the metabolism of ascorbic acid in the white cells of leukaemia as compared with normal leucocytes. In spite of abnormally high values of the vitamin-C content of the blood in cases of leukaemia, test doses of vitamin C were completely retained [966]. Butler and Cushman [967] estimated a value of vitamin C in the white cells of human leukaemia ten times that of normal leucocytes. Contradictory reports have appeared concerning the capacity of ascorbic acid to reduce the white cell count in patients suffering from leukaemia. Ralli and Sherry [345] observed no effect on the number of white cells following the intravenous injection of 600 mg. of vitamin C in a case of agranulocytosis. At this point it is of interest to indicate the higher concentration of vitamin B_1 in leukaemic than in normal leucocytes [968].

Vitamin D

In 12 children, Crowley and Taylor [969] noted an iron-resistant hypo- or normochromic anaemia associated with a low blood content of inorganic phosphorus. The administration of 2,000 I.U. of vitamin D on two occasions, with an interval of two weeks between, restored the phosphorus concentration to normal within a month; ferrous sulphate, which was prescribed during the period of vitamin administration, was then found to cure the anaemia. The effects of the dietary calcium and phosphorus and of vitamin D

on the utilization of iron was studied by Fuhr and Steenbock [970, 971, 972]. When calcium was fed in excess it was observed that the formation of haemoglobin and storage of iron were decreased, and that when the calcium : phosphorus ratio in the diet was optimal and the iron content controlled, the addition of vitamin D produced an increase in haemoglobin concentration and in total body iron content. Lack of agreement exists on what calcium : phosphorus ratio is most favourable on iron utilization, but as Cartwright [973] points out, neither a high nor a low ratio is incompatible with normal haematopoiesis if the diet contains sufficient iron, since the action of these minerals is not directly on the haemoglobin formation but on iron absorption.

Vitamin K

Normal plasma prothrombin times are usually found in haemophilia and in certain diseases in which spontaneous haemorrhage may occur, such as acute leukaemia, aplastic anaemia and thrombocytopenia. Vitamin K is ineffective in controlling the bleeding in these conditions. Patients suffering from Addisonian pernicious anaemia in relapse commonly show a considerable decrease in the plasma prothrombin concentration, which is not rectified by vitamin-K administration, but responds to liver therapy [974]. Warner *et al.* [975] observed that there resulted a prompt restoration of the plasma prothrombin to normal values following repeated haemorrhages in experimental animals.

Folic Acid

The first successful response of patients with macrocytic anaemia to synthetic folic acid was recorded in 1945 by Spies and his collaborators [976]. Five patients were treated with daily intramuscular injections of folic acid and a reticulocyte response was noted on the third day; 4 other patients to whom the compound had been administered by the oral route showed a similar satisfactory outcome. Since then there have been many reports confirming the value of folic acid in the haematological state of Addisonian pernicious anaemia in relapse. Davidson and Girwood [977] observed the transformation of the bone-marrow from a megaloblastic to a normoblastic state in 6 cases of Addisonian pernicious anaemia treated with folic acid. They obtained an excellent response from a single large dose given orally or parenterally, but reported subsequently that this was a wasteful method of administration. The effect of oral folic acid therapy was observed to be in every way comparable to that resulting from the best liver extracts as far as

the blood condition was concerned, and good reticulocytic response, a sustained rise of the haemoglobin and red cells and clinical remission of symptoms were noted [978]. Berman *et al.* [979] state that it is possible to predetermine which patients with macrocytic anaemia will respond to folic-acid therapy by recognition of the presence or absence of megaloblastic development of the erythrocytes in the bone-marrow. Davidson and Girwood [980] confirmed the view that a haematological response to folic acid will be obtained only in patients suffering from a megaloblastic anaemia; they found that when leucopenia and thrombocytopenia are part of a nutritional syndrome resulting from a deficiency of folic acid, an increase in both leucocytes and platelets will follow folic-acid administration. Enthusiasm for this form of treatment in Addisonian pernicious anaemia soon received a check when it was discovered that folic acid failed to prevent the onset of neurological changes, even when the blood remained at normal levels [981, 982]. The report of Doan *et al.* [983] is somewhat surprising; they treated a patient affected with pernicious anaemia and combined sclerosis of the spinal cord with folic acid, and observed disappearance of the paraesthesias and of Rombergism, and a return of vibratory sensation. The position is summed up by Vilter, Vilter and Spies [984]. Folic acid in doses of 10 to 15 mg. daily or 30 mg. three times a week maintained 21 patients with pernicious anaemia in haematological remission for one year. Three patients responded to an initial dose of 10 mg. daily, but 2 of them required increasing amounts daily to maintain a remission; the third received 50 mg. daily for almost a year to determine the effect of this dosage on peripheral neuritis. It was found that doses of 10 to 50 mg. daily did not prevent the development of subacute combined degeneration of the cord in 4 persons, nor did daily doses of 100 to 500 mg. arrest its progression in these patients, whereas rapid improvement followed treatment with liver extract. They conclude that an unknown factor present in liver, other than folic acid, is essential for the maintenance of the integrity of the nervous system in the subjects of pernicious anaemia; folic acid alone cannot be considered as yet a complete or satisfactory treatment for pernicious anaemia, and it should not replace liver extracts.

Hall and Watkins [985] reported that considerable variation in the rate of erythrocyte regeneration may be encountered, and in certain instances they did not obtain normal blood values until after several months of treatment with doses which they considered to be relatively large; neurological features appeared as a new manifestation two to five months after the initiation of folic-acid therapy, even while the blood picture remained at normal levels. A patient of Davidson and Girdwood proved resistant to folic-acid

therapy, although responding satisfactorily to anahaemin; a peculiar reaction to folic acid in this case was the development of severe agranulocytosis. A valuable use of folic acid is the preliminary treatment of those individuals with Addisonian pernicious anaemia who are sensitive to liver extract; methods of desensitization can be adopted while the blood state is being rectified by folic acid.

Thymine (5-methyl uracil), which has been synthesized, is one of the nucleotides in thymonucleic acid and it has been found to possess anti-anaemic properties akin to those of folic acid. Frommeyer *et al.* [986] state that a haematological response is produced by the daily administration of 4–5 grams or more in patients with pernicious anaemia in relapse. There is no exact knowledge as yet of the mode of action of thymine, but it is suggested that it is possible that folic acid may act as an enzyme or co-enzyme in the synthesis of thymine or thymine-like compounds, and that such synthesis may take place in the gastro-intestinal tract [987]. Thymine is effective for the anaemia of tropical sprue [988]. Spies [989] points out that thymine, while of great scientific interest, is of little practical importance, since the dosage required is high; it is in the neighbourhood of 1,200 times the weight of folic acid required to produce a similar response.

Synthetic folic acid has proved successful in megaloblastic anaemia in infancy [illegible] ıd Ogden [991] state that anaemias [illegible] ılood formation in the bone-marrow [illegible] under the age of 18 months. Certain criteria are postulated. A severe normochromic anaemia is present, usually but not invariably macrocytic in type, showing a wide spread in the corpuscular diameters as determined by a study of Price-Jones curves. A tendency to neutropenia exists, giant metamyelocytes (macropolyocytes) and hypersegmented neutrophils being found in the peripheral blood. The platelets are diminished and the marrow film resembles that of Addisonian pernicious anaemia in relapse; the presence of abnormal young granulocytes is a constant early finding. Splenomegaly, evidence of infection and a histamine refractory achlorhydria are all common, but not constant findings. Zuelzer [992] considers that there is complete parallelism regarding the response of this form of anaemia with folic-acid therapy to the megaloblastic anaemia of adult life; he was unable to demonstrate beneficial effects from treatment with folic acid in the other forms of anaemia of childhood which he had so far investigated.

Darby and Jones [993] demonstrated that folic acid is effective in the treatment of the macrocytic anaemia of sprue. Subsequent studies [994, 995] confirmed this finding.

Lopez *et al.* [996] classify the macrocytic anaemias with

the blood condition was concerned, and good reticulocytic response, a sustained rise of the haemoglobin and red cells and clinical remission of symptoms were noted [978]. Berman *et al.* [979] state that it is possible to predetermine which patients with macrocytic anaemia will respond to folic-acid therapy by recognition of the presence or absence of megaloblastic development of the erythrocytes in the bone-marrow. Davidson and Girwood [980] confirmed the view that a haematological response to folic acid will be obtained only in patients suffering from a megaloblastic anaemia; they found that when leucopenia and thrombocytopenia are part of a nutritional syndrome resulting from a deficiency of folic acid, an increase in both leucocytes and platelets will follow folic-acid administration. Enthusiasm for this form of treatment in Addisonian pernicious anaemia soon received a check when it was discovered that folic acid failed to prevent the onset of neurological changes, even when the blood remained at normal levels [981, 982]. The report of Doan *et al.* [983] is somewhat surprising; they treated a patient affected with pernicious anaemia and combined sclerosis of the spinal cord with folic acid, and observed disappearance of the paraesthesias and of Rombergism, and a return of vibratory sensation. The position is summed up by Vilter, Vilter and Spies [984]. Folic acid in doses of 10 to 15 mg. daily or 30 mg. three times a week maintained 21 patients with pernicious anaemia in haematological remission for one year. Three patients responded to an initial dose of 10 mg. daily, but 2 of them required increasing amounts daily to maintain a remission; the third received 50 mg. daily for almost a year to determine the effect of this dosage on peripheral neuritis. It was found that doses of 10 to 50 mg. daily did not prevent the development of subacute combined degeneration of the cord in 4 persons, nor did daily doses of 100 to 500 mg. arrest its progression in these patients, whereas rapid improvement followed treatment with liver extract. They conclude that an unknown factor present in liver, other than folic acid, is essential for the maintenance of the integrity of the nervous system in the subjects of pernicious anaemia; folic acid alone cannot be considered as yet a complete or satisfactory treatment for pernicious anaemia, and it should not replace liver extracts.

Hall and Watkins [985] reported that considerable variation in the rate of erythrocyte regeneration may be encountered, and in certain instances they did not obtain normal blood values until after several months of treatment with doses which they considered to be relatively large; neurological features appeared as a new manifestation two to five months after the initiation of folic-acid therapy, even while the blood picture remained at normal levels. A patient of Davidson and Girdwood proved resistant to folic-acid

therapy, although responding satisfactorily to anahaemin; a peculiar reaction to folic acid in this case was the development of severe agranulocytosis. A valuable use of folic acid is the preliminary treatment of those individuals with Addisonian pernicious anaemia who are sensitive to liver extract; methods of desensitization can be adopted while the blood state is being rectified by folic acid.

Thymine (5-methyl uracil), which has been synthesized, is one of the nucleotides in thymonucleic acid and it has been found to possess anti-anaemic properties akin to those of folic acid. Frommeyer *et al.* [986] state that a haematological response is produced by the daily administration of 4–5 grams or more in patients with pernicious anaemia in relapse. There is no exact knowledge as yet of the mode of action of thymine, but it is suggested that it is possible that folic acid may act as an enzyme or co-enzyme in the synthesis of thymine or thymine-like compounds, and that such synthesis may take place in the gastro-intestinal tract [987]. Thymine is effective for the anaemia of tropical sprue [988]. Spies [989] points out that thymine, while of great scientific interest, is of little practical importance, since the dosage required is high; it is in the neighbourhood of 1,200 times the weight of folic acid required to produce a similar response.

Synthetic folic acid has proved successful in megaloblastic anaemia in infancy and childhood [990]. Zuelzer and Ogden [991] state that anaemias with a megaloblastic type of blood formation in the bone-marrow are common in white children under the age of 18 months. Certain criteria are postulated. A severe normochromic anaemia is present, usually but not invariably macrocytic in type, showing a wide spread in the corpuscular diameters as determined by a study of Price-Jones curves A tendency to neutropenia exists, giant metamyelocytes (macropolyocytes) and hypersegmented neutrophils being found in the peripheral blood. The platelets are diminished and the marrow film resembles that of Addisonian pernicious anaemia in relapse; the presence of abnormal young granulocytes is a constant early finding. Splenomegaly, evidence of infection and a histamine refractory achlorhydria are all common, but not constant findings. Zuelzer [992] considers that there is complete parallelism regarding the response of this form of anaemia with folic-acid therapy to the megaloblastic anaemia of adult life; he was unable to demonstrate beneficial effects from treatment with folic acid in the other forms of anaemia of childhood which he had so far investigated.

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megaloblastic bone-marrow. When achylia persists after histamine injection, the condition is considered as Addisonian pernicious anaemia. Those showing acid and steatorrhoea are considered as sprue, and those with a dietary deficiency without achylia or steatorrhoea come under the category of nutritional macrocytic anaemia. Folic acid will relieve the anaemia of all these conditions. In the macrocytic anaemia of Addisonian pernicious anaemia, of nutritional deficiency and of sprue, Frommeyer and Spies [997] found folic acid, thymine and concentrated liver extract to be effective in treatment, but thymine was the least effective of the three. The macrocytic anaemias of pellagra and of pregnancy respond to folic acid treatment, and Spies *et al.* [998] are of the opinion that they are indistinguishable from a laboratory point of view, and group them under the nutritional macrocytic anaemias. They regard sprue and non-tropical sprue as similar entities. The macrocytic anaemia of pellagra is not due to an insufficiency of intrinsic factor, since when gastric juice from pellagrins was incubated with ground beef it produced a remission in subjects of Addisonian pernicious anaemia in relapse. The term 'macrocytic' employed as above is used in American literature synonymously with 'megaloblastic'.

As Davidson and Girdwood indicate, folic acid can safely be advocated for the initial and maintenance treatment of the megaloblastic anaemia of pregnancy, of nutritional megaloblastic anaemia, of refractory megaloblastic anaemia and of the megaloblastic anaemia of the sprue syndrome, since subacute combined degeneration of the cord very rarely develops in these conditions. Administration of folic acid, they state, can be stopped in the anaemias of nutrition and pregnancy when the blood count has attained normal values, provided a satisfactory diet is consumed; in the sprue syndrome the maintenance requirements will vary according to the course of the disease, while in refractory megaloblastic anaemia a maintenance dose is required for life, the suggested dosage being 5 mg. of folic acid daily. These authors found that some cases of the sprue syndrome and idiopathic refractory anaemia continued to have a macrocytosis and a primitive type of normoblastic bone-marrow, despite continued administration of potent parenteral liver extracts and folic acid; restoration of these persisting changes was achieved in some, but not all, by the addition of proteolysed liver. Spies [989] emphasizes the marked improvement in the general health of the patient which accompanies the haematological response to folic acid. An increase in strength and vigour and a return of appetite take place.

Folic acid has been considered ineffective in the treatment of aplastic anaemia, iron-deficiency anaemia, and the anaemia of

leukaemia, but Gendel [999] reports that remission of varying degree occurred in 3 cases of aplastic anaemia given folic acid. Satisfactory results followed the use of folic acid in the megaloblastic anaemia of cirrhosis of the liver; the results in this form of anaemia, associated with lesions of the gastro-intestinal tract, are variable [1000].

Since the leucopenia produced in monkeys and rats existing on a deficient diet could be corrected by L. casei factor, synthetic folic acid has been tried in conditions of leucopenia of various origins. Spies reported that folic-acid therapy was effective in relieving the leucopenia of certain nutritional conditions, but it did not correct the leucopenia of a number of infections or of idiopathic aetiology. The granulocytopenia produced in rats by thiourea or thiouracil can be relieved by folic acid [1001]. Newman and Jones [1002] administered folic acid prophylactically and therapeutically to counteract this complication of thiouracil therapy in man; the therapeutic qualities of folic acid remained in doubt, but large doses as a prophylactic measure did not prevent the incidence of agranulocytosis. Watson *et al.* [1003] observed an elevation of the leucocyte count in some cases of leucopenia resulting from X-ray therapy. Berry *et al.* [1004] noted a transient rise in the leucocyte count of some malnourished patients in whom leucopenia was demonstrable.

See Addendum to this page at end of book.

THE VITAMINS IN DISORDERS OF THE NERVOUS SYSTEM

Vitamin A

IT WAS formerly believed that vitamin A exerted a profound influence on the nutrition of the nervous system. Axonal, neuronic and myelin degeneration developed in the central nervous system and peripheral nerves in some animals maintained on a vitamin-A-deficiency diet. While these changes are demonstrable, their mode of production is explained in terms of bony overgrowth which damages the adjacent nervous structures by mechanical compression, distortion of the normal bone configuration, and by interference with the blood supply and with the regulation of the normal cerebrospinal fluid pressure. Vitamin A, in the growing animal, controls the activities of the osteoblasts and osteoclasts. Its presence is necessary for the deposition and absorption of bone in normal manner, and deficiency states, during the growth period of animals, are associated with disordered ossification, so that irregularities of the skull and vertebral bones develop. At the base of the skull the architectural derangement is particularly marked, bone being deposited anywhere on the inner and outer tables. In addition to this skeletal deformation, vitamin-A deficiency is responsible for retardation of growth of the skeletal system whereas, unlike the deficiency states of pyridoxine and riboflavin which stunt the growth of both the skeleton and the nervous system, the growth rate of the central nervous system remains unimpaired [1005]. The disproportion so occasioned will also contribute to the development of mechanical disturbances and secondary involvement of the nervous structures. Wolbach and Bessey state that the vitamin appears not to be concerned with the physiology of the neurone or in the formation or maintenance of myelin. Mellanby [1006] describes the osseous changes mentioned, but also puts forward the suggestion of a direct effect on the neurone attributable to lack of vitamin A. A possible explanation of the difference of reports on the action of vitamin-A deficiency on the nervous system is that the results of the experiments are greatly influenced by variations in the rate of growth of the animal.

Lathyrism

In man, a deficiency of vitamin A has been considered as a possible factor in the aetiology of lathyrism. The disease is characterized

by a spastic type of paralysis. The majority of cases occur in India, but the disorder has also been reported from France, Italy and Algeria. A greater incidence is found in the male sex.

As a rule the onset is abrupt, so that the individual may suddenly find his legs weak after a period of rest or on arising from bed in the morning. The minority of cases, associated with a gradual appearance of the disorder, complain of backache, cramp and paraesthesias of the legs; rigors and fever are other features which may be present [1007]. Walking becomes difficult because of loss of power and trembling of the legs Within a few days marked increase of the disability of the lower limbs becomes obvious. Walking is impossible without support at the stage of maximum intensity. Both limbs are simultaneously involved, and spasticity is pronounced. The subjective sensory sensations are of a transient nature. There is no objective sensory loss and, except in a few instances, no involvement of sphincter control. Muscular wasting is absent as a rule, and the mental faculties are unaffected. After the condition has persisted for some time, a degree of improvement occurs, but some muscular weakness remains, and the signs of an upper motor lesion persist Extensor and adductor hypertonus is marked. A peculiar gait is described depending on the posture of the lower extremities, the body being raised on one side by tilting of the pelvis to clear from the ground the toes of the advancing limb, which is circumducted; the gross adduction also produces a scissor-legged gait.

Although a certain amount of recovery ensues, there remains a permanent residual paresis Relapses may occur, with resulting increasing disability of the legs, and finally a paraplegia in flexion may develop. The arms are but rarely implicated. Death is usually due to an intercurrent illness; lathyrism in itself is not a fatal disease. Pathological studies are few. Buzzard and Greenfield [1008] reported degeneration of the direct and crossed pyramidal tracts and some degenerative lesions of the column of Goll.

Lathyrism was formerly considered to be attributable to toxic substances contained in *Lathyrus sativus*. The Lathyrus peas are a cheap food, and during famine years communities can exist largely on this commodity, since the plants are hardy and grow well under poor conditions Certainly the disease is often associated with the consumption of Lathyrus as the main bulk of the diet, but in such circumstances there may also be considerable inadequacy of the total food intake The existence of a toxin in *L. sativus* has been postulated and also denied. Anderson *et al.* [1009] claimed to have demonstrated toxic alkaloids in *Vicia sativa*, another type of vetch, which they considered a common contaminant of Lathyrus. This latter finding was denied by Young [1010] who reported the

frequent incidence of night blindness in the disease; he observed that lathyrism did not occur even when the major portion of the diet was composed of Lathyrus, providing vitamin A was also contained in sufficient quantity in other ingested foodstuffs. Mellanby [1011] observed in the dog the production of spinal cord lesions similar, although not identical, to those found in human lathyrism, following feeding with *V. sativa*, and to a lesser extent with *L. sativus*; these lesions were far more readily induced if the animal's diet also lacked vitamin A and carotene. He suggested that lathyrism might be attributable to a combination of a vitamin-A-deficiency state and a toxin. The possibility of inadequacy of other essential nutrients in the pathogenesis of lathyrism is raised by Denny-Brown [1012]; the absence of tryptophane in the diet may lead to a neutralization of the action of a vitamin. Rudra and Battacharya [1013] investigated the state of vitamin-B_1 nutrition in the subjects of lathyrism. The thiamine balance of their diets was found to be satisfactory, as were thiamine levels in the blood and urine. The authors, howev discovered a consistently elevated serum alkaline phosphatase, ar put forward the hypothesis that this increased phosphatase con centration may inactivate the circulating cocarboxylase; they coulc not explain the mechanism producing the phosphatase increase. The precise aetiology of lathyrism remains obscure.

Studies on Vitamin B_1 and the Vitamin-B Complex in Neurological Disease

There remain certain problems and puzzling experimental results relating to the action of vitamin B_1 on the nervous system. Thiamine alone will cure the ataxia, leg weakness and cranial nerve lesions developing in pigeons maintained on a vitamin-B_1-deficiency diet [1014]. Degenerative lesions have been demonstrated in the peripheral nerves and central nervous system in some thiamine-deficient animals. Pigs, when fed a diet adequate in all the known members of the vitamin-B complex, but deficient in thiamine, develop anorexia, vomiting, dyspnoea, cyanosis and bradycardia; no clinical or pathological evidence of involvement of the central or peripheral nervous system is, however, observed [1015]. Considerable doubt persists as to whether the neurological manifestations encountered in vitamin-B_1-deficiency states in animals are attributable to the thiamine deficiency *per se*, or to the associated lack of general food intake. On this latter basis the therapeutic action of thiamine would be due to improvement in the anorexia which accompanies the deficiency condition. Much remains to be learned, but in the interpretation of animal experiments it is

important to bear in mind the difference between an acute and a chronic vitamin-B_1 deficiency, and to distinguish between total deficiency of the vitamin and subminimal intake. In the first instance the clinical picture may vary, and the response to treatment will be greater in acute deficiency states. The early stages of vitamin-B_1 deprivation are associated with biochemical changes – increased pyruvic acid, altered oxygen consumption and a decreased respiratory quotient; while these functional changes may well be reversible with thiamine therapy, it cannot be assumed that established morphological changes will respond to this form of treatment. As an example of the difference of effect between total and incomplete absence of vitamin B_1 from the diet are the collapse and spasticity in dogs which appear under the former circumstances, and the degenerative lesions of the peripheral nerves under the latter [1016].

The rôle of vitamin B_1 in the maintenance of normal function of the human nervous system is also difficult to assess from human experiments: calf tenderness appeared at a late stage in the experiments of Williams and his colleagues [1017], and psychological disturbances were much more prominent than the delayed appearance (110 days after the institution of the deficient diet) of objective sensory signs in the lower limbs. Williams *et al.* were led to question whether lack of thiamine was the factor responsible for beriberi, and they suggested that deficiency of other members of the vitamin-B complex may be more important. A similar conclusion was arrived at by Vedder [1018, 1019], who was able to produce neurological changes in experimental animals with diets containing much vitamin B_1. It is now generally accepted that beriberi is a polydeficiency disorder. Strauss [1020] reviews the position of thiamine in relation to the nervous system. He states that while thiamine appears to be intimately concerned with the metabolism and integrity of the nervous system, other vitamins are also implicated, and that peripheral nerve lesions may result from a variety of deficiencies in experimental animals.

While vitamin B_1 has been extensively employed in the treatment of polyneuropathies of different aetiologies, this mode of therapy has been adversely criticized. Meiklejohn [1021], from a survey of the literature on the use of the vitamin in these disorders, concluded that there was no proof of any influence of thiamine in the promotion of the repair of nerve fibres which had suffered as a result of a nutritional inadequacy Walshe [1022] observed that he had never witnessed a case of polyneuritis, acute or chronic, which had shown a clear and striking response to thiamine or vitamin-B administration. What is recognized is that a neurological disturbance arising from a nutritional deficiency in the human is

never due to lack of a *single* essential nutrient. As Wintrobe *et al.* [1023] so well express the position: 'The assumption that in beri-beri only thiamine deficiency occurs, implies on the part of the victim a knowledge of the distribution of vitamins in foods and an ability to select them, which would be exceptional to say the least.'

The effects of acute riboflavin deficiency in animals differ from those of chronic riboflavin depletion [1024]. The former in the dog is attended by profound collapse, and no specific neurological lesions are demonstrable. In chronic deficiency there ensue clumsiness of gait and loss of reflexes, but little else clinically; myelin degeneration of the peripheral nerves and posterior columns of the spinal cord are demonstrable. Wolbach and Bessey [1025] question the authenticity of the view that these neurological changes encountered in the chronic deficiency state are attributable to lack of riboflavin. Stannus [1026] attaches much importance to the rôle of riboflavin in the nutrition of the human nervous system. Paraesthesias of the lower limbs, unsteadiness, weakness and objective sensory changes, he considers, may be due in part to ariboflavinosis, as well as inco-ordination of the arms and legs, diminished muscular tone, vertigo and other signs of cerebellar dysfunction; Parkinsonian features and mental upset may also be encountered in the clinical picture. The position of riboflavin as a possible agent in the production of retrobulbar neuritis is by no means established, although this possibility has at times been suggested.

Nicotinic acid in relation to pellagra has already been discussed. Thiamine deficiency in all probability accounts for the neuritic manifestations of the disease, and perhaps also for some of the mental phenomena. It is doubtful whether nicotinic-acid deficiency leads to any definite morphological changes in the nervous system, but its association with a psychotic disturbance is now recognized (p. 245).

Some of the neurological features of pantothenic-acid deficiency have been referred to under the description of that vitamin. Lesions of the peripheral nerves and spinal cord have been produced in experimental studies. Wintrobe *et al.* [1027] reported an ataxic state in pantothenic-acid deficiency in swine associated with damage to the posterior root ganglia and their axons. Pyridoxine deficiency was also found to promote similar manifestations in swine, and Wintrobe *et al.* [1028] recorded a severe microcytic anaemia, fatty infiltration of the liver and epileptic seizures in these animals secondary to lack of pyridoxine. Although other clinical features of neurological involvement are not prominent, demyelination of the peripheral nerves and posterior columns of the spinal cord are demonstrable following lack of pyridoxine. Massive

doses of pyridoxine will, in the rat, lead to areas of muscular atrophy, tremors and convulsions [1029].

Multiple Neuritis

The term 'neuritis' is used in reference to affections of the nerves which are not necessarily inflammatory in origin; 'neuropathy' is a preferable designation, but the two continue to be employed interchangeably. A classification of polyneuritis is not a simple matter, so numerous are the possible precipitating factors. As a working arrangement the following is suggested: –

A – Metabolic.
B – Toxic and Infective.
C – Chemical.
D – Miscellaneous.

A - Metabolic Neuropathy

Alcoholic Neuritis. – Chronic alcoholics are prone to develop vitamin-deficiency states, since their caloric intake in the form of alcohol is high, while their consumption of foodstuffs is inadequate; the latter condition may arise from an excessive expenditure on liquor, which leaves little money available for the normal dietary constituents, or from anorexia derived from the alcoholic gastritis. Impairment of absorption, secondary to chronic inflammatory mucosal changes, may also act in the production of a nutritional deficiency. Alcohol has no direct toxic action on the peripheral nerves, and the neuritis has been attributed to a deficiency of thiamine. Jolliffe *et al.* [1030, 1031] reported an inadequate intake of vitamin B_1 in alcoholic neuropathy, and concluded that deficiency of this vitamin was the underlying cause of the condition. The initial enthusiasm for thiamine therapy in alcoholic neuritis has become tempered in view of the accumulated evidence of the poverty of results. The observations of Meiklejohn and of Walshe have been referred to, and Brown [1032], who included also the vitamin-B complex and liver in treatment, found no greater degree of improvement as compared with a control series treated by ordinary procedures An interesting and significant finding was made by Lowry and his co-workers [1033] in paired feeding experiments in rats fed a vitamin-B_1-deficient diet: those animals receiving alcohol showed the onset of the nerve derangement at a later date than those on water only, and vitamin B_1 was found to relieve the neuropathy in both groups.

Gestational Neuritis. – Increased requirements of vitamin B_1, nausea, vomiting and perhaps also perversion of appetite have been

propounded as factors involved in the production of a thiamine-deficiency state in pregnancy, which may precipitate a polyneuritis. In the puerperium the loss of nutrients in the lactating breast may predispose to a similar state. Hypochlorhydria or achlorhydria is a common event in pregnancy, and may contribute to the tendency to vitamin-B_1 undernutrition. Berkwitz and Lufkin [1034] described degenerative changes in the peripheral nerves and in the anterior horn cells in the polyneuritis of pregnancy; the petechial haemorrhages observed in the brain and spinal cord were considered to be due to the concomitant dehydration. Gestational polyneuritis has been attributed to lack of thiamine. The most severe cases are usually found in hyperemesis gravidarum, but the neuropathy may appear after recovery from this condition or in the absence of any vomiting. Permanent paralysis may ensue, and there may be a fatal issue. Milder cases are much more common than the severe varieties. McGoogan [1035] points out that the serious examples of polyneuritis occur early in pregnancy, and may be of extreme degree, involving the muscles of respiration, and on occasions may be associated with mental confusion of the Korsakoff type. The frequency of eye signs (26·6 per cent) is also stressed by McGoogan. He recommends the administration of 50 to 100 mg. of thiamine daily, and states that therapeutic abortion is definitely contra-indicated. Posner and Hecht [1036] describe an example of the disorder in which cardiac manifestations, oedema and neuritis co-existed; the cardiac dysfunction responded dramatically to vitamin-B_1 therapy, whereas the nervous disturbance was slow to improve. Reports in the literature indicate that while the milder forms of the neuropathy recover with vitamin-B_1 therapy, the tendency to spontaneous recovery renders the evaluation of vitamin therapy a difficult matter. Response in the marked types of polyneuropathy is very slow and indefinite. As with alcoholic neuritis, the demonstration of a thiamine-deficiency state does not necessarily imply an aetiological relationship.

'Gastrogenous' Polyneuropathy. – This nomenclature was suggested by Douthwaite [1037] to signify the association of a multiple neuritis with a gastric dysfunction. It is merely a descriptive term indicating such an association, and does not necessarily imply that the underlying aetiology is the same for all cases [1038]. It has been suggested that inadequate food intake, achlorhydria, rapid evacuation of the stomach, diarrhoea, impaired absorption, and possibly increased destruction of vitamins within the alimentary tract may severally act in producing a vitamin-B_1-deficiency state, and so lead to polyneuritis Examples have been recorded following peptic ulcer, pyloric stenosis, dysphagia and tumours of the gastro-intestinal tract [1039, 1040, 1041]. Vitamin B_1 administered

parenterally appears to be effective in some, but by no means all, cases.

Diabetic neuritis and the neuritic features of pernicious anaemia are considered elsewhere.

B - Toxic and Infective Polyneuropathy

Reports on the value of vitamin-B_1 therapy in herpes zoster are far from conclusive. Investigations on post-diphtheritic neuritis have yielded contradictory results regarding the efficacy of treatment with thiamine. Wassman [1042] criticized many of the papers on this subject on the grounds of the small number of observations, the variability of the amount of vitamin B_1 administered, and the lack of control material. He produced paralysis in a group of mice by the injection of a mixture of diphtheritic toxin and anti-diphtheritic serum. The animals were divided into two equal series, one receiving 0·5 mg. vitamin B_1 intramuscularly daily from the first day, and it was found that in both groups paralysis developed at the same time and with the same frequency, and was of the same severity and duration. From his work on human subjects, Wassman concluded that a deficiency of thiamine played no part in the incidence of post-diphtheritic neuropathy, and that thiamine was not an effective therapeutic agent in the developed condition. A similar conclusion was arrived at by Donovan and Bannister [1043] who, however, claimed an improvement in the general health of patients affected with post-diphtheritic neuritis following thiamine therapy Pirzada [1044], discussing the use of vitamin B_1 in the acute varieties of polyneuritis as seen in infective and febrile disorders, stated that the efficacy of this mode of treatment is open to considerable doubt.

C - Chemical Neuropathy

Arsenic, lead, mercury and sulphonamides are among the substances which may produce a polyneuritis. There are reports of the value of treatment with vitamin B_1, but these do not seem to be sufficiently convincing to suggest that thiamine offers a specific remedy for the condition. The mode of action of arsenic, which leads to the development of polyneuritis, is not yet clear, but Peters [1045] demonstrated that vesicant substances such as dichlordiethyl sulphone and iodoacetic acid had an antagonistic action to the enzymes concerned with the further conversion of lactate in carbohydrate metabolism. The resulting effect resembled that of thiamine deficiency.

D - Miscellaneous

This is a heterogeneous group, made up of examples of polyneuritis which are associated with such diverse conditions as endocrine disturbances, serotherapy, hypertrophic polyneuritis and interstitial neuritis. Some individual cases appear to have been benefited by vitamin administration, but there is no great justification for the view that thiamine will prove of advantage as a routine measure in the majority of individuals affected with any of these forms of neuropathy. Similarly, the claims for the efficacy of vitamin-B_1 treatment in traumatic lesions of the nerves remain far from being substantiated.

WERNICKE'S ENCEPHALOPATHY

In 1881 Wernicke [1046] described a condition to which he gave the name acute superior haemorrhagic polio-encephalitis. The disorder is not of inflammatory origin, but probably is an expression of a polydeficiency state. Aetiological factors include chronic alcoholism, gastro-intestinal derangement, pernicious anaemia, neoplastic conditions, cachectic and wasting diseases such as tuberculosis, diseases associated with marked reduction of food intake and psychotic states in which the patient refuses nourishment. Campbell and Russell [1047] describe 21 cases, and in nearly all the primary disease was characterized by chronic gastro-intestinal disorder. Alcoholism, gastric carcinoma, pyloric stenosis, bowel resection and emesis gravidarum were among the primary diseases. De Wardener and Lennox [1048] present a report of 52 cases encountered in a Singapore prisoner-of-war hospital. As predisposing causes they found protracted diarrhoea in 45 cases, failure of adaptation in 3 and febrile conditions in 4. Wernicke's encephalopathy appears to develop during the course of maladies which occasion nutritional failure, and it may appear as a terminal event in many prolonged and debilitating diseases. Other deficiency syndromes, such as pellagra, nicotinic-acid deficiency, ariboflavinosis and scurvy may accompany Wernicke's encephalopathy [1049]. Wortis *et al.* determined the blood pyruvic acid in 11 cases, and the effect upon it of ingested dextrose. They found pronounced elevation of the levels, which returned to normal following administration of vitamin B_1. They concluded that the syndrome was due to an inability properly to metabolize pyruvic acid, and that prolonged treatment with the vitamin-B group of vitamins corrects the defect. Campbell and Russell stress the importance of a deficiency of vitamin B_1 and nicotinic acid, while Warrender and Lennox ascribe the aetiology of their series to a thiamine deficiency,

and employ the designation 'cerebral beriberi' as synonymous with Wernicke's encephalopathy. Jolliffe *et al.* [1050] attribute the ophthalmoplegia to thiamine deficiency, and the mental changes to lack of vitamin B_1, nicotinic acid and riboflavin. Experimentally, lesions similar to those of Wernicke's syndrome in man have been produced in pigeons on a thiamine-free diet [1051].

The pathological changes show a predilection for certain sites of the brain. These include the paraventricular grey matter of the 3rd ventricle, the mammillary bodies, the peri-aqueductal grey matter wherein are present the oculomotor and trochlear nuclei, the corpora quadrigemina and the region beneath the ependyma lining the floor of the 4th ventricle [1052]. Not all these areas may be implicated in the one case. The lesions are symmetrical, and vascular stasis and degenerative changes are evident. Involvement of other areas, such as the corpus striatum, substantia nigra, the optic nerves, and, rarely, the cerebral cortex, are described by Campbell and Biggart [1053]. Microscopically the capillaries are seen to be dilated, and show a tendency to rupture with the formation of 'ring' haemorrhages; their endothelial cells become swollen and proliferate, thus interfering with the nutrition of the part, whose parenchyma undergoes degenerative changes with reactive glial infiltration. Peripheral neuropathy and lesions of the posterior columns of the spinal cord are demonstrable in some cases.

The clinical features of Wernicke's encephalopathy are characterized by disturbances of consciousness and focal neurological signs. Clouding of consciousness may progress to actual coma, while in others drowsiness and apathy may alternate with phases of excitement and maniacal behaviour [1047]. Delirium and Korsakoff's syndrome have also been observed. Convulsions are of rare occurrence. Loss of appetite was the most frequent preliminary symptom encountered by Warrender and Lennox, and was succeeded by nausea and vomiting. Eye signs appeared early as nystagmus, diplopia and photophobia; loss of visual acuity, papilloedema, ptosis, pupillary abnormalities, complete ophthalmoplegia and retinal haemorrhages were also described by these authors, who found nystagmus to be the earliest sign demonstrable. The mental changes described by Warrender and Lennox were initiated by a sense of apprehension, which later gave way to apathy and emotional instability; excitement was encountered in a few instances. Memory defects, disorientation, confabulation and hallucinations might precede the onset of coma which, however, may rapidly develop in the absence of any of the above features as the first evidence of the disorder. Cranial nerves, other than the oculomotor nerves, may occasionally be affected, as may the pyramidal tracts. Peripheral neuropathy frequently co-exists, as does

See Addendum to this page at end of book.

ataxia. Black [1054] noted that retinal haemorrhages were common when Wernicke's encephalopathy complicated hyperemesis gravidarum.

Treatment consists of measures adopted for the relief of the primary disorder, the correction of the diet, and of the use of vitamin B_1 which, although claims are made for cure by this vitamin alone, is best administered in conjunction with other members of the vitamin-B complex. Korsakoff's psychosis not uncommonly persists in recovered cases, and the ataxia may remain uninfluenced by therapy.

SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD

The descriptive nomenclature of this disorder takes no cognizance of the peripheral nerve and cerebral lesions which are also present. The association of the condition with pernicious anaemia has long been appreciated. Rundles [1055] reviews the condition and points out that the commonest and usually the earliest type of neurological disorder in pernicious anaemia is due to involvement of the peripheral nerves, and secondarily the posterior columns of the spinal cord. Muscular weakness and tenderness, paraesthesias and impairment of sensation nearly always appear before the features of lateral column disease, and ultimately the picture is a combination of lower and upper motor neurone disorders accompanied by the sensory phenomena. Foster [1056] described the pathological findings in the examination of the peripheral nerves in pernicious anaemia; evidence of degeneration was manifested by reduction in the myelin sheaths and axis cylinders, degeneration of myelin, increase in Schwann cells and endoneural connective tissue, axonal reaction changes in the ganglion cells of the posterior root ganglions, and degenerative changes in the intramedullary course of the afferent posterior root fibres. Dynes and Norcross [1057] studied 92 patients with pernicious anaemia; 21 had unmistakable peripheral neuritis in combination with combined system disease, and 22 had the clinical signs of the latter without peripheral neuritis. It was found that about 50 per cent of the neuritic group had gastro-intestinal symptoms on admission, as compared with 21 per cent of the other group. They consider that paraesthesia and dysaesthesia of the extremities, and the frequent impairment of vibratory and proprioceptive sensibilities cannot irrefutably be accredited to peripheral nerve involvement.

While vitamin deficiency may be important, Dynes and Norcross state that it does not act alone in the production of the neurological lesions. Rundles discovered no therapeutic response in the lingual,

haematological or neurological manifestations of pernicious anaemia following the administration of the common vitamin-B components. Aring and Spies [1058] reported relief of pain and improvement of muscular function in the neuritis of pernicious anaemia when vitamin B_1 was prescribed in large dosage; only a limited degree of improvement resulted, beyond which this form of therapy exerted no further effect. Ungley [1059] obtained no beneficial response from treatment with vitamin B_1. Folic acid and thymine do not prevent the development of subacute combined degeneration of the cord in pernicious anaemia, nor relieve it once it has developed [1060]. Davidson and Girdwood [1061] treated three cases of the disorder with folic acid; in two no subjective or objective improvement accrued, while in the third there was definite and rapid deterioration of the neurological features in spite of marked response of the blood picture. Evidence is as yet not forthcoming for any decided advantage in the prescribing of vitamin supplements in the treatment of subacute combined degeneration of the cord Rundles reported that those patients who were not treated with supplementary yeast or vitamin-B products showed no difference in the rate and degree of neurological recovery as compared with those who received these substances

VITAMIN E IN NEUROLOGICAL DISORDERS

Vitamin E has been employed in the treatment of amyotrophic lateral sclerosis (motor neurone degeneration). Bicknell [1062] treated patients with this disorder with whole wheat-germ oil; of 4 cases, 2 died, but some clinical improvement was noted in the remaining two Weschler [1063, 1064] reported improvement with this mode of treatment. In a subsequent study [1065] normal serum tocopherol values were demonstrated in subjects with untreated amyotrophic lateral sclerosis, and the blood level was observed invariably to rise after oral administration of tocopherols, irrespective of whether or not the patient showed clinical improvement; intramuscular injection, without simultaneous oral administration, produced a fall in the serum tocopherol level. Weschler and his co-workers concluded that a simple vitamin-E deficiency does not exist in this disease. While there are other records of claims for a beneficial action of vitamin E in motor neurone degeneration, the bulk of available evidence would appear to refute the claim for any therapeutic action of vitamin E in the disorder. Shelden [1066], Denker and Schneiman [1067], Ferrabie *et al.* [1068] and Fitzgerald and McArdle [1069] are among those who obtained negative results. Worster-Drought and Shafar [1070] treated 25 cases with vitamin E

See Addendum to this page at end of book.

in the form of tocopheryl acetate (30 mg. daily) or wheat-germ oil capsules (equivalent to 18 mg. tocopherol daily); only two showed some improvement, and it was observed that the patients affected with bulbar palsy showed the most rapid deterioration. Vitamin E has proved disappointing in motor-neurone degeneration and cannot be considered to be indicated in the treatment of this affliction.

In a similar manner, the few encouraging reports on the value of vitamin E in muscular dystrophies are far outweighed by the negative results obtained by other investigators. Fleischman [1071] could discover no effect of alpha-tocopherol upon the creatine-creatinine excretion in cases of amyotonia and progressive muscular dystrophy, and he considered that this indicated a fundamental difference between the nutritional muscular dystrophy of animals and the muscular dystrophic syndromes of man. De Jong [1072] was unable to demonstrate any definite beneficial effects following vitamin-E therapy. Shanks *et al.* [1073] also obtained negative results, and Minot and Frank [1074] concluded that the administration of vitamin E to patients with muscular dystrophy was an unnecessary and useless procedure. Milhorat and Bartels [1075] suggest that the utilization of tocopherols in patients suffering from muscular dystrophy is enhanced by the simultaneous administration of inositol.

In a study of tabes dorsalis Reese and Hodgson [1076] could find no evidence of any consistent dietary deficiency. Stone [1077] treated 18 cases of tabes dorsalis with vitamins B and E; 17 were also given thiamine hydrochloride by the intrathecal route. The patients had previously been treated with routine antisyphilitic therapy without arrest of the progress of the disease. Stone claimed that improvement in gait, muscle tone, strength and co-ordination was obtained, and that there was better bladder control and reduction in the lightning pains. Administration of large doses of tocopherol were not attended by any beneficial effect in disseminated sclerosis [1078]. It would appear that the case for the use of vitamin E in neurological disorders is far from proven, and that the somewhat isolated reports of improvement succeeding tocopherol therapy in nervous diseases, other than those mentioned above, can hardly be accepted as of great significance without further controlled investigations.

Vitamins in the Therapeusis of Neurological Disease

Epilepsy. – The demonstration by Chick and her colleagues [1079] that pigs deprived of pyridoxine developed fits suggested the use of this vitamin in the treatment of the disorder. Spies *et al.* [1080]

noted improvement in idiopathic epilepsy when pyridoxine was administered intravenously, but Fox and Tullidge [1081] reported that trials of the vitamin in varying doses did not effect any change in the incidence of fits, nor any alteration in the mental or physical states of their epileptic patients. Fox and Tullidge concluded that it seems unlikely that pyridoxine, even in large doses, would be of value in epilepsy.

An untoward reaction ensuing during the treatment of epileptic patients with dilantin sodium is gingival hypertrophy. Kimball [1082] expressed the opinion that this benign hyperplasia was attributable to a deficiency of vitamin C induced by the medication. No influence on the vitamin-C nutrition of animals was noted by Gruhzit [1083] following the administration of the drug, and Merritt and Foster [1084] arrived at a similar conclusion regarding human beings. The swelling of the gums is not related to the ascorbic-acid levels of the plasma or to the utilization of the vitamin. When low serum levels of ascorbic acid are encountered in epileptic subjects, they are usually found to arise from an inadequate consumption of foodstuffs rich in the vitamin

Muscular Dystrophy and Motor Neurone Degeneration. – Pyridoxine has been employed in the treatment of pseudohypertrophic muscular dystrophy and motor neurone disease. Spies *et al.* [1080] and Antopol and Schotland [1085] reported beneficial results from this mode of therapy, but Doyle and Merritt [1086], McBryde and Baker [1087], and Denker and Scheinman [1088] are among those who were unable to detect any evidence of a satisfactory response. The number of observers who have presented negative findings is far in excess of the others who suggested an advantageous effect, and it would appear that pyridoxine therapy possesses little or no value in these disorders.

Muscular Weakness. – Spies *et al.* [1089] obtained improvement in the muscular power and relief of fatigue in pellagrins following pyridoxine administration and after they had been vigorously treated with nicotinic acid, thiamine and riboflavin. Rosenbaum and Soskin [1090] reported noteworthy increase in muscular power when pyridoxine was given intravenously to one patient with neurasthenia, 3 patients with hyperthyroidism and 4 with ulcerative colitis No effect was demonstrable in 1 patient with myasthenia gravis or in 3 patients with malnutrition. The differences of the response are puzzling, and make any assessment of this type of action a difficult matter.

Extrapyramidal Lesions. – Monkeys under experimental conditions of B avitaminosis developed a mask-like facies, increased salivation and lachrymation and a forward stooping posture with propulsion [1091]. Lewy *et al.* [1092] studied the neurological features of

pellagra, and noted that 5 out of 50 pellagrins manifested features of mild Parkinsonism. Pyridoxine has been tried in the treatment of paralysis agitans and of the post-encephalitic Parkinsonian syndrome. Encouraging results were recorded by Jolliffe [1093] and by Spies and his co-workers [1080], the latter forming the opinion that the arteriosclerotic group was least benefited. Baker [1094] and Meller [1095] were also impressed by the response to pyridoxine. Loghlin *et al.* [1096] treated 12 cases of long-standing paralysis agitans with large amounts of the B vitamins; 2 showed subjective improvement. Ten patients with paralysis agitans were treated with saline; initial improvement was found in 9 cases, which persisted throughout the period of treatment in 3 instances. These investigators stress the difficulties of evaluation of therapeutic effects, and did not consider that paralysis agitans was causally related to any specific vitamin deficiency. The psychological effects of treatment were evidenced by the control group. Disappointing results were the experience of Zeligs [1097] and Barker *et al.* [1098].

Vitamins Administered Intrathecally. – Vitamins have been administered by intrathecal injection for therapeutic purposes. Subarachnoid instillation of thiamine will promote rapid recovery of vitamin-B_1-deficient rats. A study of the vitamin content of the cerebrospinal fluid [1099] revealed no evidence of riboflavin which, if introduced by the cisternal route, rapidly disappeared. Nicotinamide was present, the average concentration being 69 micrograms per cent, but no cocarboxylase could be demonstrated; the latter, if injected into the subarachnoid space, rapidly passed into the blood. Para-amino-benzoic acid was not detected. Sinclair [1100] found a wide fluctuation in the thiamine concentration of the cerebrospinal fluid, ranging from zero levels to 6·5 micrograms per cent. The ascorbic-acid estimation in the spinal fluid yielded a value of 0·55 mg. to 0·75 mg. per 100 c.c. [1101]. Wirth [1102] claimed that an increased content of ascorbic acid exists in the cerebrospinal fluid in cases of the post-encephalitic Parkinson syndrome and that intravenous administration of ascorbic acid was attended by amelioration of the condition. Stern [1103] advocated the intrathecal injection of vitamin B_1 for the relief of pain in a variety of diseases, and observed improvement with no ill-effects from this mode of therapy. These results were not confirmed by Aring and Spies [1104], and Odom and McEachern [1105] reported moderate signs of meningeal reaction following the introduction of thiamine into the subarachnoid space. Stern also stated that disseminated sclerosis responded to this form of treatment, and Stone [1106] considered it a valuable adjuvant in the management of tabes dorsalis, although his results are somewhat obscured

by the simultaneous use of other therapeutic measures. Pyridoxine hydrochloride was given by the subarachnoid route by Stone [1107] for a variety of diseases, including chorea, meningomyeloradiculitis, poliomyelitis, Korsakoff's syndrome, disseminated sclerosis, neurosyphilis and sciatica. Combination of pyridoxine with thiamine and artificial pyrexia, Stone considered to be a useful adjunct in the treatment of neurological disorders. Robbie [1108] reported lack of success with intrathecal vitamin-B_1 injections in a series of chronic degenerative neurological diseases.

Trigeminal Neuralgia. – Various vitamin preparations have been suggested for the relief of trigeminal neuralgia. Nicotinic acid was reported to relieve the paroxysms of pain. Adams and Robinson [1109] employed nicotinic acid in doses of 50 to 75 mg. twice to four times daily; 7 cases were treated, and in all of them improvement, sometimes amounting to complete relief, was obtained. The rationalization of the effect was the vasodilatation produced. Furtado and Chicorro [1110] used nicotinic acid by the intravenous route, and in some cases by oral administration also; in successful cases relief of pain persisted for months after only a few injections. During a paroxysm of pain an intravenous injection was attended with immediate cessation of the pain. Thiamine has been advocated in tic douloureux by Borsook *et al* [1111] and by Borson [1112], but its efficacy is denied by Rose and Jacobson [1113.]

Headache. – A number of reports have appeared recommending the use of nicotinic acid in the treatment of headache. Atkinson [1114] recommended a course of intravenous injections, followed by oral maintenance dosage Goldzieher and Popkin [1115] employed sodium nicotinate, 100 mg being administered intravenously. They studied 100 consecutive patients suffering from severe headache and attempted to minimize psychological factors. Relief of the headache was obtained in 75 of the cases and appeared to be correlated with the degree of peripheral flush The authors recommend this form of symptomatic treatment in severe idiopathic headache, migraine and in the headache which follows lumbar puncture. In contrast to the very rapid effect of intravenous injection, Zeligs [1116] reported a delay of thirty to forty minutes before the intractable headache of malarial subjects showed a response to oral medication; not all the cases were benefited, but 50–100 mg of nicotinic acid orally administered is suggested as a valuable measure for the relief of such headaches when they are of daily occurrence

Vitamin B_1 has been used in the treatment of migraine [1117]; an intramuscular or intravenous injection of 60 to 120 mg. is given for the immediate attack, and 30 to 90 mg daily for preventive purposes. Thiamine has been recommended in the symptomatic

treatment of other varieties of pain of diverse origin. Goodman [1118] obtained relief of pain in cases of herpes zoster by large parenteral doses of vitamin B_1, but Rattner and Roll [1119] found this mode of therapy to be ineffective.

The above list is by no means an exhaustive one. Vitamins have been prescribed in almost every type of disease of the nervous system. The reports of a positive nature are usually counterbalanced by negative statements of others, and the general conclusion, which would appear a justifiable one, is that, with but few exceptions, vitamin therapy does not occupy an important position in the therapeutic armamentarium of the neurologist.

The Vitamins in Neuropsychiatric Conditions

Deficiency of vitamins may lead to mental disorder, but the latter state may in itself occasion a defective dietary intake, so that on the existing mental derangement there may be superimposed those features attributable to the deficiency itself. These features may be not only functional alterations, but also organic changes, as in the cases described by Clarke and Prestcott [1120]. In the elucidation of the aetiology of a neuropsychiatric upset, it is important to search for physical signs indicative of vitamin deficiency. Thiamine, nicotinic acid, riboflavin, pantothenic acid and pyridoxine are the important factors whose deficiency causes psychologic upset [1121]. Vitamin-C deficiency is a common concomitant of mental disorders, but does not appear to bear any causal relationship.

A common manifestation of vitamin-deficiency states is the neurasthenic syndrome. The studies in man on experimental thiamine-deficiency diets have already been described. The presenting symptoms may be extremely varied, and since there may be but little, if any, clinical evidence of a deficiency state, and since psychotherapeutic measures may produce some degree of improvement, diagnosis becomes a matter of considerable difficulty. Treatment with thiamine or the vitamin-B complex will serve as a diagnostic measure. The frequency of occurrence of similar states not originating from vitamin deficiency must be fully appreciated.

Pellagra. – The neuropsychiatric manifestations of pellagra may appear in an insidious fashion, and may be mild and vague in character. More pronounced and eventually obvious psychotic features appear in the later stages. While evidence of mental derangement occurs as a rule only after the somatic signs have developed, there are examples in which the neuropsychiatric features were the sole manifestation. Meyersburg [1122] calls attention to simulation of senile psychosis by pellagrous encephalopathy in the aged, and emphasizes the importance of main-

tenance of adequate food intake in the normal elderly individual as well as in the senile invalid; when a satisfactory food consumption is not possible, supplementary vitamins should be prescribed. Freeman [1123] advises a policy of suspecting every psychotic patient, whose feeding habits are faulty, as a potential pellagrin. Bacillary dysentery is a not uncommon complication in patients in mental institutions, and will predispose to nutritional failure. This aspect is stressed by McLester [1124]. Hardwick [1125] describes cases of pellagra complicating psychosis.

Nicotinic-Acid-Deficiency Encephalopathy. – A syndrome has been segregated which is attributed to an acute nicotinic-acid deficiency. Cleckley *et al.* [1126] recorded the remarkable response to nicotinic-acid administration in a series of 19 stuporose patients, and indicated that profound clouding of consciousness may be the sole presenting feature. Jolliffe and his colleagues [1127] further reported on this state, which they named 'nicotinic-acid-deficiency encephalopathy'. This syndrome may also develop in association with other signs of a deficiency disorder, and in pellagra, beriberi and Wernicke's syndrome. The additional manifestations recorded by Jolliffe *et al.* were cog-wheel rigidity of the limbs, uncontrollable sucking and the grasp reflex. Vitamin-B_1 administration is attended with an almost 100 per cent mortality rate, whereas treatment with nicotinic acid greatly reduces the incidence of a fatal issue, although residual phenomena commonly persist. Sydenstricker and Cleckley [1128] reported examples of mental confusion which were relieved by nicotinic acid; these included stupor, disorientation, maniacal features, hallucinations and delusions. Gottlieb [1129] describes five cases of the acute nicotinic-acid-deficiency syndrome. Mental confusion, disorientation and restlessness were among the clinical signs and, in some, evidence of a vitamin-deficiency state was forthcoming from the physical examination. Gottlieb points out that elderly people living alone and in poor circumstances, chronic alcoholics, and those suffering from gastro-intestinal disorders are particularly prone to the disorder. Diagnosis may not be easy on purely clinical grounds, but the possibility should always be borne in mind in elderly or debilitated patients who suddenly develop mental abnormalities or disturbances of consciousness. The 'Saturday-night drunk' admitted to hospital in a comatose condition may, in actual fact, be suffering from a nicotinic-acid-deficiency encephalopathy. The dietary history, when obtainable, is of value, but the response to nicotinic-acid therapy will usually clinch the diagnosis. Treatment consists of administering 100 mg. of nicotinic acid or 30 mg. of nicotinamide hourly for 10 doses in the first two days by mouth or by stomach tube. When necessary, the parenteral route is employed, the vitamin being administered as sodium

nicotinate in 100 mg. doses. For several days thereafter 500 mg. daily are prescribed, followed by 25 mg. thrice daily [1130]. Other vitamins also should be prescribed simultaneously, and if nicotinic-acid treatment be accompanied by marked vasomotor disturbances, it should be replaced by nicotinamide.

The Korsakoff Syndrome. – The Korsakoff syndrome was described in 1890 [1131]. The characteristic features are a loss of memory for recent events and a tendency to confabulate, with disorientation for time, place and person. A frequent, but not invariable concomitant, is peripheral neuropathy. Chronic alcoholism is the commonest aetiological factor, but the syndrome is encountered in association with a variety of conditions, such as diabetes mellitus, arteriosclerosis and toxic states. Rosenbaum and Merritt [1132], while stressing the importance of vitamin therapy, state that a vitamin-deficiency state cannot be the sole factor concerned, since half of their 22 cases who were placed on no special dietary treatment recovered. Bowman *et al.* [1133] observed that 11·8 per cent of their series recovered while receiving a basal diet with no additional intake of vitamins. Other reports available indicate a beneficial response to thiamine, but in view of the spontaneous recovery in some instances the rôle of thiamine or other vitamin deficiency in the production of Korsakoff's psychosis remains undetermined. In the recovered state of Wernicke's syndrome, Korsakoff's psychosis may be evident as a residual condition. Jolliffe *et al.* [1134] reported 12 such examples in a group of 13 patients suffering from Wernicke's syndrome who had been treated with large amounts of vitamin B_1 and other vitamins; no further benefit was obtained by continued thiamine therapy. Such observations add to the complexity of the problem of aetiology.

Delirium Tremens. – While there exist certain features in the condition of delirium tremens which are indicative of a nutritional disorder, the results of vitamin therapy have yielded little to implicate a definite nutrient factor in the aetiology. Maizner and Krause [1135] reported the satisfactory use of nicotinic acid in one case of delirium tremens. On the other hand, Rosenbaum *et al.* [1136] found that in 14 cases of the disorder the average duration of the mental upset was almost a day longer than in a group receiving no vitamin therapy; they conclude that nicotinic acid may actually exert a deleterious effect on the malady, and that its use is unwarranted except in the presence of a specific nicotinic-acid-deficiency state Spies and his colleagues [1137] also reported negative results with nicotinic-acid therapy. Claims have been advanced for the use of vitamin B_1 in delirium tremens. Kiene *et al.* [1138] and Kloster [1139] recommend intravenous thiamine injections. Rosenbaum *et al.*, however, concluded that once the disease has

developed, vitamin B_1, liver extract, or brewers' yeast was without influence in shortening the duration of the illness. An interesting observation was made by Wortis *et al.* [1140, 1141], who found subnormal levels of ascorbic acid in the blood and cerebrospinal fluid of patients suffering from delirium tremens, whereas no diminution was apparent in alcoholic addicts in whom mental and neurological changes were absent.

Neurological Disorders Produced by Prolonged and Pronounced Dietary Restriction

Following the liberation of large numbers of men from prison camps at the close of the Second World War, many examples of damage to the nervous system were observed. Analogous conditions were witnessed in Madrid during the civil war in Spain [1142, 1143]. These conditions, which were superimposed on a chronic nutritional deficiency state often complicated by dysentery and malaria, have been reviewed by Denny-Brown [1144]. The following syndromes have been described: -

(1) Retrobulbar neuritis (2) Spinal ataxia (3) Spastic paraplegia. (4) Burning feet. (5) Deafness (6) Laryngeal paralysis. (7) A myasthenic bulbar syndrome

Beriberi and pellagra were not uncommonly encountered, but as such do not enter into the present discussion.

Retrobulbar Neuritis. - This may occur alone or in combination with any of the other syndromes, or with other evidence of deficiency states [1145, 1146]. As a rule the condition develops slowly, but the onset may be very rapid Dimness of vision, most marked in the centre of the field, appears in both eyes and shows a variable degree of progression, but does not produce complete blindness. The visual upset reaches a stationary stage after several weeks, beyond which no further deterioration occurs, and in some cases improvement, even to normal levels, is noted Denny-Brown observed that relapse was frequent after an attack of dysentery. Scotometry reveals a central scotoma, which often includes the blind spot A mild papillitis or temporal pallor, often with a crescentic zone of pigmentation on this side of the disc, may be evident, but in the mild cases no abnormality can be detected on ophthalmoscopy. Cases in which the visual defect was most marked showed a total pallor of the disc and a white cuff surrounding the vessels [1147]. Macular degeneration is noted in many cases [1148, 1149] Spillane [1150] points out that retrobulbar neuritis may be found in beriberi, pellagra, Wernicke's syndrome and hyperemesis gravidarum. The association of malnutrition with amblyopia has been recognized for a considerable time. Moore [1151] reported a syndrome of

partial optic atrophy, ataxia, mental disturbance, glossitis, angular stomatitis and scrotal eczema in native school children in Nigeria. Similar syndromes have been described by others. Wilkinson and King [1152] recorded a group of cases of amblyopia in the population of Hong Kong; there was concentric constriction of the fields of vision, and satisfactory response was obtained to nicotinic acid, riboflavin or dried-yeast therapy. The resistance of the retrobulbar neuritis of captivity to yeast, riboflavin, nicotinic acid or thiamine administration renders the position of a vitamin-deficiency state difficult to interpret, although crude extracts of yeast and liver were observed to exert beneficial effects in the mild or early cases. Denny-Brown emphasizes the importance of tryptophane in the diet, lack of which he considers to be as important as lack of vitamins. There exists the possibility of a toxin which is able to exert its effects in chronic malnutritional states, in the absence of the neutralizing action of an essential nutrient constituent. Attention has also been directed to possible interference with biosynthesis in the alimentary tract or absorption therefrom. Hsu [1153] discovered changes in the nervous system in 13 subjects who had died as the result of wasting disease associated with dysentery and tuberculosis. Denny-Brown concluded that retrobulbar neuritis, spinal ataxia, spastic ataxia and spastic paraplegia represent isolated occurrences of components which are included in the picture of pellagra Further work is necessary before the exact nature of the aetiological factors, and the influences which decide the particular localization of the lesion in the nervous system, can be determined. The above remarks apply to the other varieties of malnutritional neurological derangement of this series.

Spinal Ataxia. – All gradations of disturbances of gait were encountered. Loss of vibration sense was evident in the lower and occasionally in the upper limbs, and, in less severe degree, proprioceptive sensibility was affected. The commonest finding in the examination of the reflexes was loss of the ankle-jerks. Other features which may be encountered in the 'captivity cord syndrome' were paraesthesias, impairment of touch and pain sensations, retrobulbar neuritis, partial laryngeal paralysis, and wasting, tenderness and weakness of the muscles. Denny-Brown expresses the view that the signs originate from damage to the spinal cord rather than from a peripheral neuropathy. Walters *et al.* [1147] state that a reasonable degree of recovery occurs in these cases in contrast to the poor response of the spastic paraplegic disorder.

The Spastic Syndrome. – In this syndrome, signs of a lesion of the pyramidal tracts are manifest. A stiff-legged and perhaps scissor gait develops. Denny-Brown suggests the identity of this condition with that of lathyrism. Some mental disturbance may appear in the

early stages, but does not persist. As with the other syndromes, all degrees of combination between the different members of the group may be found.

Burning Feet. – This symptom complex is also referred to as painful, aching, happy, electric and hot feet. Landor and Pallister [1154] described the syndrome in inmates of local jails in Malaya. Simpson [1155] noted the frequency of pellagra and ariboflavinosis in such cases. Both legs are affected simultaneously, and the pain is worse at night, often interfering with sleep. Cruikshank [1156] divides the subjective sensory disturbances into two types. In the first there is a dull ache, initially intermittent, and later persistent and more pronounced; the other form appears as sharp, shooting pains superimposed on the dull ache. Exercise and cold relieve the symptoms. Only a few cases show alterations of the reflexes, and Harrison [1157] reported lessened sensitivity to light touch and pain, and impaired appreciation of vibratory and thermal stimuli. Hyperaesthesia of the feet may be marked. Substances rich in the vitamin-B complex and nicotinic acid proved effective in treatment, but not thiamine or riboflavin alone Calcium pantothenate has also been employed [1158], either orally or by the parenteral route; 20–100 mg. daily usually suffices.

Deafness and Laryngeal Paralysis. – Deterioration of hearing is a gradual process, and is usually accompanied by tinnitus. Deafness is bilateral; it is of the nerve type, and varies in severity. The tympanic membranes are normal, and vertigo is not a feature.

An interesting finding is that of laryngeal paralysis. Alteration or loss of voice develops secondary to paralysis or paresis of the vocal cords.

Myasthenic Bulbar Paralysis – As the name implies, the ocular and glosso-labial-pharyngeal-laryngeal muscles become readily fatigued and weak after exercise and towards the end of the day. Ptosis, dysphagia and dysarthria appear, the facial and neck musculature are involved, and the limbs may also be affected in some cases From former descriptions of this variety of disorder Denny-Brown offers the benign nature of this form – no case was fatal after many years – as an important differentiating feature from ordinary myasthenia gravis; he refers to 3 cases under the care of Major P. R. Graves, in which physostigmine was without benefit, whereas parenteral thiamine in doses of 50 mg. daily completely relieved all the symptoms within one week.

CHAPTER TWENTY-THREE

THE VITAMINS IN ENDOCRINOLOGY

Diabetes Mellitus

VITAMIN DEFICIENCY states may be evident in diabetic patients and yield to specific treatment with the vitamins concerned while adjustment of the diabetes has not as yet been established. Rudy and Hoffman [1159], for example, observed pellagrous dermatological lesions in some diabetic patients for which nicotinic-acid therapy proved effective while the diabetes remained uncontrolled. Joslin *et al.* [1160] point out that the diabetic diet is rich in vitamins since it contains liberal portions of vegetables, fruits, meat, eggs, milk and cereals. They state that, while it is difficult to decide whether the disease necessitates an increased requirement of the vitamins, it is advisable to allow a little more than is considered sufficient under normal circumstances. Diminution or absence of hydrochloric acid, possible hepatic derangement and the susceptibility to intercurrent disease in the maladjusted case of diabetes will increase the vitamin requirements. The indiscriminate use of vitamins in diabetes should not, however, be encouraged.

Vitamin A

Ralli and her associates [1161, 1162] claimed that individuals affected with diabetes have excessive amounts of carotene in the blood in the post-absorptive state and that, following the administration of carotene, the blood-carotene level rises to unusually high levels and remains elevated for an unduly long time. This anomaly was attributed to an inability of the liver adequately to convert the provitamin into the active form. Brazer and Curtis [1163] discovered a high incidence of poor dark adaptation in juvenile diabetics which was corrected by the administration of vitamin A, but not by carotene. Kimble *et al.* [1164] criticized the conception of difficulty in the conversion of carotene to vitamin A in the diabetic. In a group of 116 unselected diabetics, all possible types of deviation of vitamin A : carotene relationships were observed, the predominant form being a low vitamin A : low carotene ratio. The latter was particularly apparent in the older patients and in those who suffered from an infectious process. Least pronounced of any trend was towards a high carotene level with deficient vitamin-A concentration in the blood, a relationship formerly assumed to be characteristic of diabetes. Deficient intake, defective

absorption, liver disease or sepsis will be accompanied by an effect on the plasma-vitamin-A values, while exaggerated ingestion of vitamin-A-containing foodstuffs, hyperlipaemia and renal disease may lead to elevated vitamin-A and carotene levels. Diabetic carotinaemia was relatively uncommon in the series of Kimble and her associates, who concluded that there was no blood picture of the vitamin-A or carotene concentrations which could be considered peculiar to the diabetic.

Vitamin B_1 and the Vitamin-B Complex

The results obtained from animal experiments of the action of thiamine on the blood sugar are conflicting. Varying opinions have been expressed as to the influence of vitamin B_1 on the blood-sugar level after an injection of insulin, but there is general agreement that it is without effect on the blood sugar in the normal human subject. Somerfeld-Ziskind *et al.* [1165] concluded that thiamine chloride exerted no beneficial action in arousing a patient with protracted coma resulting from insulin shock. Vitamin-B deficiency is not uncommon in the untreated diabetic since excessive loss of the vitamins occurs as a consequence of the polyuria It is advisable to prescribe vitamin B for a preliminary period when a diabetic patient first comes under observation, in an attempt to replenish his depleted stores.

Quite a different aspect is the question of possible benefit accruing from the administration of vitamin to the individual with controlled diabetes. Vorhaus *et al* [1166], Biskind and Schreirer [1167] and Dienst *et al.* [1168] are among the investigators who claim a valuable action from the conjunction of thiamine and insulin in therapy; improvement in carbohydrate metabolism and reduction in the dosage of insulin required are said to result. Joslin *et al.* consider that the basis for the conclusion reached regarding the advantageous action of vitamin B_1 as propounded in the existing publications is open to question, and their own studies would appear to negative any beneficial effect of thiamine on the blood sugar or insulin requirements Owens *et al.* [1169] concluded that thiamine hydrochloride had no value in the well-controlled diabetic condition, and Lawrence and Oakley [1170] were in agreement with this view.

Little change in glucose tolerance has been discovered with deficiency or excess of vitamin B [1171]. Kaufman [1172] found that thiamine had no effect on the level of the blood sugar in diabetic patients. An important communication by Sydenstricker *et al.* [1173] drew attention to the fact that when the carbohydrate of the diet is rapidly increased and an increased amount of insulin

given, clinical signs of a vitamin-B deficiency may develop; the explanation offered was that the rapid metabolism of carbohydrate in diabetic patients treated with insulin is accompanied by corresponding rapid depletion of the co-enzymes, thus producing avitaminosis. *Feston and Laughlin [1174] sum up the position* regarding the vitamin-B complex in the adequately nourished individual whose diabetes is well *controlled; it is of no value in* altering the course of the disease or in reducing the insulin requirements.

Vitamin C

Contradictory reports exist regarding the effect of vitamin C on the tolerance of glucose, and the influence of this vitamin on carbohydrate metabolism has not yet been clearly elucidated. Schroeder *[1175] described a more pronounced fall in the blood* sugar with vitamin C and insulin than with insulin alone, while Crandon *et al. [1176]* found that *the glucose-tolerance curves and* the sensitivity to insulin were within normal limits in vitamin-C deficiency states experimentally induced in human volunteers. Owens *et al.* [1177], in a study of the blood-ascorbic-acid level of 125 patients of low economic status with controlled diabetes, found a markedly higher average blood-ascorbic-acid concentration than that of 50 unselected controls. These investigators [1178] were also unable to discern any effect on the severity of the diabetic state resulting from the administration of large doses of ascorbic acid and *criticized previous reports of the efficacy of vitamin C in* this direction, since former workers disregarded the fact that the tolerance of diabetics to carbohydrate improves with treatment; they consider that this improvement had been wrongly attributed to *the effect of the vitamin.*

Diabetic Neuritis

An excellent survey of diabetic neuropathy has been presented by Rundles [1179]. As a preliminary it is necessary to exclude peripheral nerve lesions of other aetiology which occur as an incidental disorder in the course of diabetes mellitus. Most diabetics who suffer from neuropathy have an antecedent period of months' or years' duration of ill-managed treatment and the evidence is in favour of the resulting metabolic imbalance occupying the leading rôle in its production. This was well demonstrated in two cases reported by Root and Mascarenhas [1180]. Diets excessive in calories and vitamins were taken during the period preceding the onset of acute neuropathy in one case and in the other the condition

followed failure to continue treatment with controlled diet and insulin. Hyperglycaemia, loss of weight and severe neuropathy may result even when the vitamin intake is large. Diabetic neuritis may arise in mild as well as in severe grades of diabetes. Infections

Rundles and Epstein [1181] reviewed 100 cases of diabetic neuropathy. Neuritis was present in 54, myelopathy in 26, encephalopathy in 4, encephalomyelopathy in 5 and neurogenic bladder disturbances in eleven. Rundles points out that the spinal nerve roots and the autonomic nervous system may be involved. Diabetic neuropathy is a generalized neurological disorder. The cerebrospinal fluid changes may include an increase in total protein without cellular reaction and a change in the colloidal gold curve indicating, according to Root and Mascarenhas, that the central nervous system is the chief site of the lesion in the syndrome.

The position of vitamin-B deficiency in the aetiology of diabetic neuropathy has been the subject of much discussion. Wohl [1182] and Fein *et al.* [1183] were among those who considered that avitaminosis B_1 was the responsible factor. Rundles was unable to discern any deficiency of the vitamin-B content of the diet of his patients and lingual or cutaneous signs indicative of a vitamin-B-deficiency state were rarely encountered in his series of 125 cases. Jordan [1184] observed only one example of a deficient dietary in an investigation of a group of 63 subjects suffering from diabetic neuropathy. A vitamin-deficiency state produced by means other than that of inadequate intake has been postulated by some observers; faulty absorption, increased metabolic requirements and increased loss of the water-soluble vitamins as a result of the polyuria were considered the operating mechanisms, but Rundles maintains that this view has remained unsubstantiated. An interesting experiment was conducted by Lowry and Hegsted [1185]. Dogs rendered diabetic by injection of alloxan showed no increased tendency to develop signs of thiamine deficiency; the action of thiamine was not perceptibly impaired and the vitamin-B_1 requirements of the animals were less than those of the normal controls.

The reports in the literature on the response of diabetic neuropathy to thiamine are conflicting. Rundles criticizes many of them on the grounds of the use of different criteria in diagnosis, the lack of appreciation of the results obtained by diabetic therapy alone, and the inherent difficulties in distinguishing the effects of metabolic abnormalities possibly due to vitamin deficiency from those produced by the diabetes itself. Needles [1186] studied six cases of

diabetic neuritis before and after therapy with thiamine hydrochloride; in none of them was any improvement noted and in two progression of the neurological disorder had occurred. Rundles has observed progressive advancement of the peripheral neuropathy in spite of the administration of large doses of vitamin B_1, orally and parenterally, and he witnessed no improvement from any form of treatment in the absence of satisfactory control of the diabetes. Nicotinic acid also proved ineffective and the addition of brewers' yeast produced no beneficial effect.

A peculiar phenomenon is the first appearance of the neuropathy a short time after control of the diabetic state has been established or an accentuation of an existing neuropathy under these circumstances. Although Sydenstricker *et al.* [1187] suggested that the increased carbohydrate utilization which followed insulin treatment in the early stage of the disease might precipitate a vitamin-B deficiency, Rundles, however, was unable to accept this theory as the explanation of the sequence of these events.

The conclusions arrived at by Rundles are that effective control of the diabetes is the first requirement in the treatment of diabetic neuropathy, and that vitamin supplements are without effect except in the presence of clinical indications apart from the neuropathy itself.

The Thyroid Gland

Vitamin A. – The relationship of vitamin A to the thyroid gland is a difficult matter to assess in view of the conflicting evidence which has been presented on the subject. There appears to be little agreement on the effect of vitamin A on the state of the thyroid gland. Remington *et al.* [1188] from experiments in rats concluded that vitamin-A deficiency is not an aetiological factor in the production of simple goitre; they state there is an increased requirement for the vitamin in hyperfunction of the gland probably corresponding to the increased metabolic rate, and a corresponding lesser need for vitamin A occurs in thyroidectomized rats, but a deficiency of the thyroid hormone does not affect the ability of the animal to utilize carotene. Drill and Truant [1189] administered supplements of vitamin A to thyroidectomized rats receiving a diet devoid of the vitamin and found that this prevented the appearance of xerophthalmia; supplements of carotene were ineffective for this purpose in the thyroidectomized rat and the authors concluded that the thyroid gland plays an important rôle in the conversion of carotene to vitamin A. Certainly carotinaemia has frequently been described in association with myxoedema. Escamilla [1190] reports 7 consecutive cases of untreated myxoedema in which carotinaemia

co-existed. He suggested that this may explain the yellowish colour of the skin so often seen in this condition. Treatment with thyroid extract soon removed the carotinaemia.

Cod-liver oil has been suggested as of value in the treatment of thyrotoxicosis [1191] but Drill [1192] points out that the presence of iodine in the oil must be taken into consideration. In view of the reputed antagonism of vitamin A to the hormone of the thyroid gland, claims have been advanced for the value of the administration of the vitamin in exophthalmic goitre, but Korenchersky *et al.* [1193] were of the opinion that the beneficial effects of the vitamin in some experimental and clinical cases were probably due chiefly to the removal of the relative vitamin deficiency present in these cases. Drill, who reviews the subject of vitamin and thyroid interrelationships, considers that simultaneous administration of vitamin A and thyroxin will partially prevent a rise in the basal metabolic rate, although it will not lower the high metabolic rate once it has been established by thyroid feeding. It is generally thought that the vitamin-A requirements are increased in hyperthyroidism, and low blood levels of the vitamin and of carotene are often found in this disorder, returning to normal values following successful treatment of the thyrotoxicosis. Drill interprets the increased vitamin-A concentration found in the liver in hyperthyroidism as evidence of the thyroid activity increasing the conversion of carotene to the vitamin in excess of that occurring under normal circumstances; the contrary effects observed in hypothyroidism he considers to be added evidence for this view.

Vitamin B. – Hyperthyroidism involves an increased requirement of vitamin B_1. Drill [1194] observed a diminution of the thiamine content of the livers and kidneys of rats receiving 100 mg. of desiccated thyroid gland daily, even when these hyperthyroid animals were receiving 500 micrograms of the vitamin per day. Sure and Buchanan [1195] showed that thiamine administration prevented the weight loss produced in animals by as high a daily dose as 0·2 mg of thyroxin. Drill also refers to the increased requirements of pyridoxine and pantothenic acid in hyperthyroidism and points out that, if sufficient yeast is given to thyroid-fed animals, the loss in weight will be prevented and the amount lost in the hyperthyroid state will be replaced. The anorexia and loss of weight are caused or accentuated by the associated vitamin-B deficiency. Drill and Hays [1196] demonstrated that the hepatic damage produced in experimental hyperthyroidism is in part dependent on the intake of vitamin B and that a diet of high vitamin-B content delays but does not prevent the appearance of abnormal hepatic function.

Moderate and prolonged thiamine deficiency not infrequently

lowers the metabolic rate, whereas severe and rapid thiamine depletion rarely diminishes the metabolic rate. Williams and Kendall [1197] from their experiments on two healthy women, existing on a diet adequate in all respects except in vitamin B_1, concluded that the thyroid hormone is less effective in promoting the metabolic activity of the organism in a state of thiamine deficiency; thyroid was administered and in the period of thiamine restriction the metabolic rate fell, but assumed high values when the thiamine intake was liberally increased.

Williams and his colleagues [1198] demonstrated increased pyruvic-acid levels in the blood in thyrotoxic subjects; abnormalities of the pyruvic-acid curves of the blood were also evident after the intravenous injection of 50 grams of glucose. These authors attributed the thiamine-deficiency state to loss of the vitamin in the sweat, faeces and urine, to the augmented combustion of food, and possibly to the inability of thyrotoxic subjects adequately to store thiamine in view of the hepatic and muscular disorders so commonly associated with the malady. A beneficial response in hyperthyroidism from thiamine administration has been reported [1199, 1200]. Williams *et al.* observed no impairment of phosphorylation of thiamine in thyrotoxicosis, but consider that the use of the vitamin is of distinct advantage in the treatment of the disorder.

The aminobenzoic acids have a goitrogenic effect in rats [1201] and, of these, para-aminobenzoic acid is the most potent in this respect [1202], but less so than thiouracil. Both para-aminobenzoic acid and thiouracil produce marked hyperplasia, basophilia and the appearance of 'thyroidectomy' cells in the anterior hypophysis [1203]. Berman [1204] used para-aminobenzoic acid in 6 cases of thyrotoxicosis and obtained good results; the weight increased, the nervousness was lost, the basal metabolic rate returned to normal and the pulse rate was reduced.

Drill and Overman [1205] demonstrated that in experimental hyperthyroidism some deficiency symptoms persisted after administration of thiamine, and that they were not alleviated until pantothenic acid and pyridoxine were prescribed. Fishberg and Vorzimer [1206] observed that in 8 hyperthyroid patients who were receiving the usual dose of thiouracil for approximately 8 weeks, the administration of 200 mg of pyridoxine daily by mouth effected an increase of the average white count of between 1,500 and 2,000 cells per c.mm. The parenteral injection of 200 mg of pyridoxine hydrochloride resulted in an increase of 1,800 granulocytes per c.mm. within two hours in one patient whose count had dropped to 400 granulocytes per c.mm. Piney [1207] also draws attention to the dramatic effects he has obtained in the treatment of thiouracil

neutropenia with the intravenous injection of 100 mg. of pyridoxine, more than two doses rarely being required.

Vitamin C. – Hyperthyroidism increases the vitamin-C demands of the body but it is not yet established what inter-relationships exist between ascorbic acid and the thyroid hormone, although an antagonistic action has been suggested. Lewis [1208] noted that, with a constant content of vitamin C in the diet, thyrotoxic patients prior to operation showed a lesser urinary output of vitamin C than normal, and that, following operation, the urinary excretion of the vitamin increased. These observations were substantiated by Spellberg [1209]. The possible value of vitamin C in the treatment of toxic reactions of thiouracil medication is raised by Boyd and Cornell [1210].

Vitamin D. – In hyperthyroid states disturbances in calcium metabolism have been noted. While the calcium and phosphorus levels of the blood remain normal, there ensues an increased excretion of calcium through the gastro-intestinal and urinary tracts. Urinary calculi and metastatic calcification are rare events in thyrotoxicosis, so that Puppel *et al.* [1211] consider that no danger is associated with the use of a high calcium and high vitamin-D diet as a pre-operative measure, a routine which they had employed for several years. With this mode of therapy, they state, the abnormality of calcium metabolism is prevented, and none of their patients developed a thyroid crisis They were also impressed by the smoother course of the patient prior to operation [1212].

Thyroid Medication – Shapiro [1213] found that oral thyroid medication was not accompanied by an increase in the plasma prothrombin time. Adequate allowances of all the vitamins are essential when thyroid is prescribed, and especially so when dietary restrictions are simultaneously enforced.

The Sex Organs

Vitamin A. – Evans and Bishop [1214] found that in experimental animals a diet poor in vitamin A produced abnormalities in the ovaries even in the presence of good growth and apparent health; the Graafian follicles did not mature or rupture in normal fashion. The alterations in the structure of the vaginal epithelium in avitaminosis A led Simpson and Mason [1215] to employ the vitamin in the treatment of senile vaginitis and these authors reported very favourable results. Irregularities of oestrus have been noted in the rat [1216] and there is lack of desire to mate in states of deficiency of the vitamin. When mating does occur conception may not take place, and if it does, foetal resorption may ensue [1217]. Evans [1218] showed that male rats fed diets low in vitamin A, but

doxin may impair the function of the adrenal cortex, while para-aminobenzoic acid has been reputed to exert a protective influence over the adrenal medulla. Goldheizer, who reviews this subject, points out the occurrence of marked pathological lesions in the suprarenal cortex in some examples of nicotinic-acid deficiency. Following adrenalectomy in black rats, stimulation of hair growth and of melanin pigmentation ensues when the rats have been maintained on diets deficient in the filtrate factors of vitamin B; the greying of fur due to deficiency of the filtrate factor was reversed by adrenalectomy [1237].

A high concentration of vitamin C is found in the suprarenal cortex and medulla. Ascorbic acid was originally isolated from the adrenal gland. Vitamin C is considered to be an essential factor in the maintenance of the integrity of the adrenal cortex, since degenerative lesions and haemorrhages may develop therein during the course of scurvy. Kutchell and Mitchell [1238] observed a fall in the content of ascorbic acid in the adrenal gland subsequent to its stimulation. The injection of the corticotrophic hormone produced a rapid fall in the vitamin-C concentration of the suprarenal, so that within one hour the value was reduced by more than 50 per cent of the original level [1239]. Exposure of the animal to stress resulted in a similar effect, which was, however, not evident in the hypophysectomized animal. It is possible that vitamin C is an actual part of the constitution of the cortical hormone. Long discovered that epinephrine causes within an hour of its parenteral administration a decrease in the adrenal ascorbic-acid content in normal rats, but not in rats three days after hypophysectomy. According to Long, changes in the adrenal ascorbic acid and cholesterol concentrations can be used as indicators of cortical activity. The former is probably directly related to the secretion of the hormone, while the latter reflects the reservoir of the precursor of the hormone.

Epinephrine administration increases the excretion of vitamin C but conflicting reports exist as to the alleged improved pharmacological response obtained when epinephrine is injected together with the vitamin. While a low vitamin-C urinary excretion may occur in Addison's disease, this association is by no means always encountered. When present it may be an expression of altered renal function since normal plasma-ascorbic-acid levels have been noted when urinary excretion is low [1240]. The pigmentation of Addison's disease has been suggested to be related to vitamin-C metabolism. The vitamin will produce a reduction in the colour of melanin *in vitro*, and will inhibit pigment formation from dopa but the results obtained in the relief of the pigmentation of Addison's disease in man by the use of ascorbic acid have not infrequently been disappointing.

See Addendum to this page at end of book

the latter may be superimposed on an established disorder of the heart of other aetiology; anorexia, increased basal metabolism and disturbances of the gastro-intestinal absorptive mechanisms consequent on venous congestion may account for the development of vitamin-B_1 deficiency in cardiac failure. It would not seem that vitamin-B_1 deficiency is a common complication of heart failure [1254]. The use of thiamine in cardiac disease for its 'tonic' effects on the heart is open to question. It is quite a different matter to prescribe the vitamin in cardiac affections which are present in association with an inadequate intake of thiamine.

Goodhart a[illegible] addicts, who p[illegible] renal disease, [illegible] or of deficiency disease. There was minimal evidence of cardiovascular disturbances in this group but, in the remaining 65 who manifested symptoms of dietary deficiency, electrocardiography revealed evidence of cardiac dysfunction in 47 per cent, and clinical evidence of cardiac derangement was discovered in 32·3 per cent. Other disorders which result in conditioned vitamin-B_1 deficiency may similarly be reflected in cardiac abnormalities; its possible association with thyrotoxic heart disease is worth bearing in mind. On the other hand, vitamin B_1 and the vitamin-B complex have proved ineffective in the treatment of the cardiac affection of myxoedema [1256].

Swenson [1257] introduced a method of estimating the circulation time by the intravenous injection of 5 c.c. of a preparation containing 10 mg. each of thiamine hydrochloride and riboflavin, 5 mg. of pyridoxine hydrochloride, 50 mg. of calcium pantothenate and 250 mg. of nicotinamide, dissolved in 5 c.c. of sterile isotonic saline. He stated that the taste experienced was intense, abrupt and unmistakable, and that the normal value of the arm to tongue circulation time was from 9·8 to 10·3 seconds. The intravenous injection of thiamine is not without danger Vitamin B_1 has been used in the treatment of ischaemic neuritis, but is unlikely to prove of any value.

Beriberi Heart Disease

Wenkebach [1258] described the pathological changes in the heart of beriberi. Hypertrophy and dilatation are evident, the enlargement being more pronounced in the right cardiac chambers, while the left side of the heart may be very small. The expansion of the right auricle may be so marked as to reduce the wall to paper thinness, and great dilatation of the conus arteriosus may occur. That the right-sided lesion alone is not consistently present was demonstrated

by Weiss and Wilkins [1259], who observed a general hypertrophy in 9 of 30 cases. Blankenhorn *et al.* [1260] reported dilatation of both sides of the heart in one case, and in two others hypertrophy was also present. The microscopic appearances are those of hydropic degeneration of the myocardial fibres and intercellular oedema with an increase of collagen, but the cardiac hypertrophy is not due to oedema of the heart muscle. Blankenhorn *et al.* describe the changes encountered in the central, peripheral and autonomic nervous systems – degenerative lesions of the cells of the nervous sympatheticus and in the tracts of the lateral horn in the upper cervical segments of the cord, damage to the spinal cord roots, and advanced degeneration of the vagal nerves and some of the peripheral nerve trunks.

The time required for the development of beriberi heart disease is variable. The experiments of Williams *et al.* [1261, 1262] on induced vitamin-B_1-deficiency states in human volunteers would seem to indicate that a deprivation period of at least three months is necessary, but Blankenhorn *et al.* point out that many factors, such as the degree of activity and presence of complicating disease, will influence the time interval. Chronic alcoholism is responsible for the majority of cases of beriberi heart disease in America and Britain. Early symptoms are palpitation, breathlessness on exertion and tachycardia. Weiss and Wilkins [1259] emphasized certain features. Tachycardia, they stated, was followed by bradycardia; gallop rhythm, pulmonary congestion, bounding arterial pulsation, arterial 'pistol sounds', engorgement of the veins, a warm skin and oedema of the legs were present in established cases. They stressed the occurrence of a rapid circulation rate, even in the presence of congestive failure. Jolliffe [1263] also drew attention to the increased or normal blood velocity, and was of the opinion that a mild polyneuritis is usually a feature, and that in some instances rapid circulatory collapse may ensue with or without previous signs of circulatory failure. The description of Weiss and Wilkins would [illegible]

[illegible]

[illegible]

[illegible]

pheral vasodilatation are not necessary features of the clinical picture. Blankenhorn [1265] considered that the traditional signs of beriberi heart disease – rapid circulation, enlargement of the right heart and 'pistol shot' murmur – are not infrequently absent, and she advanced the following criteria: –

(1) Enlarged heart with normal sinus rhythm
(2) Dependent oedema.
(3) Elevated venous pressure.

(4) Peripheral neuritis or pellagra.
(5) Non-specific changes in the electrocardiogram.
(6) No other cause evident.
(7) Gross deficiency of diet for three months or more.
(8) Improvement and reduction of heart size after specific treatment, or autopsy findings consistent with beriberi.

Hibbs [1266] concluded that enlargement of the heart is not to be expected in the majority of cases of beriberi heart disease and that thiamine deficiency may be the cause of almost any type of cardiac arrhythmia; he found that both left and right ventricles [illegible] involved in the congestive heart failure of beriberi and that [illegible] in treatment. Casanova [1267] reported [illegible] condition. Thiamine therapy may be [illegible] the size of the heart rapidly diminishing and the [illegible]raphic abnormalities disappearing. Some patients with irreversible cellular changes may show but little response. As Hibbs indicates, the disorder must be treated energetically to prevent secondary irreversible damage or death.

The changes in the electrocardiogram are variable and non-specific. Changes in the T wave, and low amplitude of all the waves, are common. Among other changes which have been encountered are prolongation of the P-R interval, inverted T_4, auriculo-ventricular dissociation and auricular fibrillation [1268].

It is obvious that the diagnosis of beriberi heart disease may readily be missed, unless the possibility is borne in mind. An important point is that the clinical picture is not usually characteristic, and any combination of signs may exist. Inability to find any apparent cause for a cardiac disorder should raise the possibility of beriberi heart. A history of dietetic deficiency and signs indicative of a vitamin-deficiency state are of great help in establishing the nature of the underlying cause, and the response to thiamine therapy will clinch the diagnosis.

Vitamin E

Houchin and Smith [1269] induced a muscular dystrophy in rabbit
and found that in this condition the animals were resistant to cardia
glucosides. They concluded that the sudden death which occurr
in the advanced stages of the disorder was directly due to cardi
failure. It was found that vitamin-E administration had no eff
on normal hearts, but was considered to exert beneficial effects
cases of cardiac failure and of angina pectoris [1270, 1271]. I
doubtful whether these reports afford sufficient evidence for utili
tion of the vitamin in affections of the heart [1272]. According

Gullickson and Calverley [1273] the changes in the electrocardiogram in cattle on vitamin-E-free diets appear to indicate a decrease in the functional activity of the myocardium in the terminal stages of the deficiency. Ensor [1274] noted no apparent differences in the electrocardiograms of rats deprived of vitamin E as compared with those of a control series, except for a slight widening of the QRS complex in 5 of the 15 deprived rats.

See Addendum to this page at end of book.

THE VITAMINS IN OPHTHALMOLOGY

Vitamin A

Night Blindness. – The photoreceptor substance in the rod cells of the retina is visual purple (rhodopsin), which is composed of a carotenoid linked to a protein. Vitamin A is the precursor of the carotenoid. On exposure to light rhodopsin is bleached, and regeneration takes place in the dark. Deficiency of vitamin A is reflected in a decreased rate of regeneration of the visual purple. The rods are concerned with vision in a dim light, and since the sensitivity to light at the particular stage is determined by the concentration of the amount of photoreceptor substance present, in hypovitaminotic A states vision in the dark and dark adaptation are impaired. Night blindness has long been associated with lack of vitamin A, but other conditions such as retinitis pigmentosa, choroiditis and glaucoma may show a degree of night blindness as one of the symptoms. It is not to be expected that vitamin-A therapy will prove of value in night blindness in the absence of a vitamin-A deficiency. Such a deficiency may arise from defective intake, defective absorption (as in the steatorrhoeas and intestinal disease), or defective utilization (as in hepatic dysfunction). The rapidity of development of night blindness will be influenced by the tissue reserves of the vitamin prior to the onset of the deficiency, so that young age-groups may demonstrate the condition within a shorter space of time than adults. Incidental disease and pregnancy and lactation may hasten the appearance of night blindness.

Dark adaptation has afforded a measure of the vitamin-A status of the body. A large number of different methods have been evolved; their degree of accuracy has been the subject of considerable criticism and has tended to invalidate the test. Recently developed procedures have proved satisfactory. The subject is further discussed on p. 18.

The psychological basis of most of the cases of night blindness in Britain has been demonstrated [1275, 1276]. Attempts to produce an unusually good degree of night vision by the intake of large quantities of vitamin A have proved unsuccessful. The compulsory fortification of margarine with vitamin A in Britain protects against the development of night blindness resulting from a pure dietary deficiency.

Colour Blindness. – Reports have periodically appeared claiming improvement of colour blindness from the use of vitamin A. These have been criticized, and it has been suggested that such improve-

ment as does occur results from re-education rather than from vitamin therapy. Caddan [1277] employed vitamin A in daily doses of 75,000 I.U. and also prescribed vitamin-B complex and iodine; he noted an improvement in the degree of colour blindness. Negative effects were obtained with vitamin-A therapy by Elder [1278] and Briggs and Butler [1279]. There would appear to be little justification for the use of vitamin A in the treatment of colour blindness.

Conjunctival Changes. – The integrity of the epithelial structures being dependent on adequate vitamin-A content of the tissues, the conjunctiva offers a means of identifying vitamin-A deficiency. Keratinization of the conjunctivae occurs and, at a later stage, xerosis due to involvement of the lachrymal passages and cessation of secretion of the mucous cells of the conjunctival epithelium. Bitot's spots are grey or light yellow in colour, appearing as small discrete elevations which are placed laterally to the cornea; Nicholls [1280] describes their origin as a slight thickening and pigmentation of the conjunctiva of the sclerotics. The thickening and pigmentation increase, and accumulations of heaped-up epithelial cells arise; they appear as 'a dab of chalk paste striated with a pin'.

A peculiar pigmentation of the conjunctiva has been reported by Pillat [1281] in conditions of vitamin-A deficiency. A light-brown pigmentation pervades the conjunctiva; the pigment is melanin. Such a finding appears to be rare in Western countries, and even in the East not all examples of this form of pigmentation are due to vitamin-A deficiency; only 72 per cent of a series of patients exhibiting this sign were found to be deficient in vitamin A [1282].

As the deficiency progresses, the xerophthalmia becomes more pronounced and the conjunctiva is wrinkled and thickened. A stringy conjunctival discharge is marked, and adhesions may develop between the eye and the lids. Photophobia, blepharospasm and pain may be marked

Kruse [1283] recommended the use of the slit lamp in the detection of early changes in the conjunctiva indicative of vitamin-A deficiency. He stated that a loss of transparency, succeeded by thickening and then by increased vascularity of the conjunctiva occurred; the thickening was general, but most marked laterally to the cornea, and later the thickening appeared as a distinct elevation. Berliner [1284] criticized these changes as manifestations of avitaminosis A, since he could find no other evidence of a deficiency of this vitamin, and he ascribed the conjunctival lesions to simple senile changes. No correlation was found by Anderson and Milam [1285] between the severity and incidence of conjunctival changes as detected by the slit lamp and the level of vitamin A in the diet or blood plasma.

Keratomalacia. – This is a rare and advanced stage of the ocular effects of vitamin-A deficiency. The cornea is affected; its transparency is lost and softening develops. The surface is denuded and ulceration appears with ultimate perforation. Secondary infection ensues and blindness is almost inevitable. In adult subjects the progression of the eye lesion is gradual, so that xerophthalmia precedes the keratomalacia; however, in the young the condition may develop with great rapidity in the absence of any prior xerotic changes.

Vitamin A in other ocular conditions. – Sjögren described a condition in women of the menopause characterized by dryness of the eyes and mouth, due to deficient lachrymal and salivary secretion. This condition, keratoconjunctivitis sicca, is associated with arthritis in a large percentage of cases. Some consider it a manifestation of vitamin-A deficiency, but vitamin-A therapy would not appear to produce significant improvement. The occurrence of congenital ocular malformations in the young of vitamin-A-deficient female rats may have a bearing in human studies. Warkany and Schraffenberger [1286] described the formation of retrolental fibrous tissue, colobomata, and other malformations in experiments in rats under these circumstances.

Vitamin B

Nutritional Amblyopia. – Retrobulbar neuritis has been described in deficiency diseases in Africa and in the Far East in association with other manifestations of lack of vitamins. Attention has been directed to the condition in view of its frequency in prisoners of war. An optic atrophy is common, but in some cases of long duration no change may be seen in the optic fundus; some macular lesions may be evident, associated with obliterative changes in the arterial branches [1287, 1288]. A central scotoma is the usual field change noted, but peripheral constriction may be present [1289]. The position of vitamin deficiency in this condition is not yet clear, but it would appear that a general avitaminosis, particularly of the vitamin-B complex, acts in its production in association with toxins. The experimental findings of Knapp and Blackberg [1290] are interesting. These investigators observed lesions, resembling those of senile arteriolar sclerosis in man, in the eyes of rats suffering from various forms of malnutrition; inadequate caloric intake, deficiency of vitamins A, B, or D consistently produced increased light reflex, pallor and uniform attenuation of the arterioles along their entire course. Treatment of nutritional amblyopia must be instituted at an early phase, or the visual impairment becomes permanent. A balanced nutritious

diet supplemented with vitamins should be ordered and liv injections administered.

Deficiency of thiamine has been incriminated in tobacc amblyopia. This disorder has responded to vitamin-B_1 therapy [1291]. Carroll [1292] records the cure of tobacco-alcohol amblyopia with vitamin B in a woman, who continued to consume alcohol during treatment and did not improve her diet.

The Ocular Manifestations of Ariboflavinosis. – By means of slit-lamp examination Sydenstricker *et al* [1293] observed proliferation and engorgement of the limbic plexus as the earliest lesion of riboflavin deficiency in man. Circumcorneal injection and corneal vascularization came to be looked upon as diagnostic of riboflavin deficiency. In typical cases large numbers of capillary loops invade the normally avascular zone between the limbic plexus and the sclerocorneal junction. As the period of riboflavin deficiency extends, there is an increasing penetration of the cornea from the periphery by the capillary loops, so that all degrees of corneal vascularization may occur. Accompanying these changes are subjective sensations which include photophobia, burning, itching of the eyes and lachrymation. The explanation of these vascular reactions has been that the avascular cornea is normally dependent for its metabolic requirements on an enzyme system for whose formation riboflavin is essential. Deficiency of riboflavin necessitates that the cornea depend for its nutrition on the blood stream; hence the ingrowth of small blood vessels

There has been considerable criticism of the specificity of these signs and also of the interpretation of what signs constitute the vascular reaction of riboflavin deficiency Circumcorneal injection or engorgement of the limbic plexus must be differentiated from actual invasion of the cornea with newly formed blood vessels. Ferguson [1294] describes the vascular structure of the limbic plexus; in ariboflavinosis fine vessels run from the apices of existing limbic loops into the cornea, and these new vessels anastomose with one another to form further loops from which in turn fresh vessels develop, and the process is repeated Under normal circumstances the limbic vessels are collapsed, but they become engorged with any trivial stimulus The vascular changes characteristic of ariboflavinosis should be considered only when new capillaries are observed budding from the apices of the terminal loops and running radially into the cornea, and only when these changes are equally present in both eyes [1295] Many reports have been issued regarding the high incidence of vascularization of the cornea and its non-association with or lack of response to riboflavin [1296, 1297, 98]. The different criteria employed by different observers are source of difficulty. Vail and Ascher [1299] believe that much of

the so-called corneal vascularization is merely engorgement of the normal pericorneal plexus.

The effects of exposure to excessive light on the eyes were investigated by Lowry and Bessey [1300]. They concluded that brilliant, continuous illumination with incandescent lamps did not augment the changes resulting from riboflavin deficiency, and that the vascular reaction of the eyes, so prevalent among those exposed to excessive sunlight, did not result from local destruction of riboflavin. In a series of subjects, who received only 0·47 mg. of riboflavin daily in their diet for five weeks, corneal vascularization did not develop [1301], and in 4 patients, who had subsisted on a diet containing 0·21 mg. riboflavin per 1,000 calories for 288 days, similar negative results were obtained [1302]. Corneal vascularization may appear in patients receiving ample amounts of riboflavin, but individual variations in the requirements of the vitamin appear to exist, and the influence of other factors, such as pantothenic acid and pyridoxine, in the metabolism of riboflavin must be taken into consideration. The picture is further complicated by the fact that deficiencies, other than that of riboflavin, may produce the vascular response in animals, and these include deficiency of vitamin A, of zinc, and of the amino-acids, lysine and tryptophane. From a study of corneal vascularity in personnel of the Royal Air Force, Lyle *et al.* [1303] concluded that riboflavin is not the only nutrient concerned in the prevention of corneal vascularization. Duke-Elder [1304] described in long-standing cases concentric opacities in the cornea and aneurysmal-like dilatations of the vessels, especially those on the scleral portion of the limbus; these vascular changes may be so large as to simulate haemorrhages. Riboflavin therapy in the cases of lesser severity produced dramatic, rapid emptying of the vessels.

It would appear that riboflavin deficiency is not always associated with ocular changes. When these occur, they are diagnostic of ariboflavinosis only if the criteria mentioned above are found, and only if a satisfactory response to riboflavin administration is obtained. The association of other signs of deficiency of riboflavin renders the possibility of a riboflavin deficiency as the cause of the ocular manifestations more likely, as does a history of low dietary intake of the vitamin. The position of other nutrient factors, which may be responsible for the corneal vascularization and of other vitamins which interact with riboflavin, requires further study.

Riboflavin in Other Ocular Disorders. – Conjunctivitis, blepharitis, cataract and interstitial keratitis have been observed in rats on riboflavin-deficient diets [1305, 1306]. Conjunctivitis, phlyctenular conjunctivitis and eye strain in man have been treated with riboflavin, but it is not to be expected that this mode of therapy

should be effective in the absence of an existing riboflavin deficiency.

In rosacea, Doggart [1307] described greyish-white infiltrates in the cornea, particularly in the superficial layers. Large vessels, arising from the ocular conjunctiva, were associated with these infiltrates, and corneal ulceration might ensue. The similarity between rosacea keratitis and the corneal lesions of riboflavin-deficient rats suggested the use of riboflavin in its treatment. Johnson and Eckardt [1308] reported the satisfactory results of riboflavin therapy in 32 out of 36 cases of rosacea keratitis, and postulated a deficiency of the vitamin in the aetiology of the condition, since a low dietary content of riboflavin was noted, and the possibility of impaired absorption was put forward; a series of cases of active and inactive keratitis of other origin was treated for over a year with large doses of riboflavin, but failed to respond. Fish [1309] was unable to substantiate a beneficial reaction from riboflavin therapy in rosacea keratitis. Cosgrove and Day [1310] considered that various types of corneal lesions recovered more rapidly when riboflavin was administered.

Rubeosis iridis in a non-diabetic subject suffering from pernicious anaemia was observed to clear up under treatment with riboflavin [1311]. Stannus drew attention to the similarity of rubeosis iridis and certain manifestations of ariboflavinosis, and suggests the rôle of deficiency of the vitamin in the causation of the condition.

The association of cataract with riboflavin deficiency in young pigs was observed by Wintrobe *et al.* [1312] In rats riboflavin deficiency also produces cataract, and administration of the vitamin prevents the lenticular changes. It does not seem that riboflavin is of any value in the treatment of cataract in the human subject [1313].

Vitamin C

A high concentration of ascorbic acid is present in the ocular fluids and tissues. Within the lens and aqueous fluid the very high values are striking. Henkes [1314] demonstrated that the greatest concentration is found in the subcapsular cortex of the lens, and the least in the nucleus; in guinea-pigs affected with scurvy, ascorbic acid was first lost in the cortex, but was quickly replenished with appropriate feeding. Evacuation of the aqueous humour in the normal animal is followed by rapid restoration, and the tension is restored perhaps even to levels greater than normal; in scorbutic animals this procedure is associated with a slower restoration of the aqueous humour, and a delay in the development of normal tension. Vitamin C would appear to be concerned in the maintenance of normal fluid exchange in the eye [1295].

Cataract in human beings is associated with a marked reduction

absence of vitamin C *in the lens*. Rados [1315] could find no
dence of a vitamin-C deficiency in 200 patients affected with
:aract, and considered that there was insufficient evidence to
licate any relationship of hypovitaminosis C with the causation of
:aract. Transparency of the lens was not dependent on the
amin-C saturation of the body. The reports concerning vitamin-C
:rapy in cataract would appear to indicate little value for this
de of treatment, although a few observers have claimed a degree
improvement. The rôle of vitamin C in the nutrition of the lens
nains to be determined.

[n human scorbutic states haemorrhages may occur into the
ijunctiva, the eyelids and the fundus. Retro-orbital haemorrhage
y produce proptosis. It is doubtful *whether other ocular mani-*
:ations in scurvy can be ascribed to lack of vitamin C; cataract is
: found in scurvy, except as a coincidental condition.

Vitamin-C therapy was of no avail in retinitis pigmentosa [1316].
markable improvement was reported by Lyle and McLean [1317]
the treatment of corneal inflammation and ulceration with
ge doses of vitamin C (500 mg. intravenously daily) in conjunc-
n with local treatment.

Vitamin D

ılar Cataract. – The association of a zonular cataract with
unges in the teeth and bones is a recognized syndrome. Accord-
ly it has been assumed by some that a deficiency of vitamin D is
responsible agent. This is so only in an indirect manner. Tetany
feature of many *of the cases. The factor which produces the*
ticular changes is the hypocalcaemia. While tissue cultures of
lens fibres remain unaffected by a big increase of the calcium
centration of the nutritional fluid, a small decrease rapidly
duces death and opacification of the lenticular cells.

Cod-liver Oil. – *While vitamin* A *can be absorbed into* the body
owing its instillation into the conjunctival sac, it is probable
t any beneficial response obtained from the external use of cod-
r oil in corneal inflammations and injuries is largely dependent
its lubricating qualities.

Vitamin K

vas observed that retinal haemorrhages occurred more frequently
newborn infants with low prothrombin values than in infants
h normal *values, and it* was reported that marked reduction in
incidence of these haemorrhages could be produced by the
ninistration of vitamin K to the mother during labour, or before

the actual onset of labour. Maumenee *et al.* [1318], however, could find no relationship between the extent of the retinal haemorrhage and the degree of hypoprothrombinaemia. With the abatement of the first wave of enthusiasm for vitamin-K therapy, and following the demonstration by Sanford *et al.* [1319] of lack of association between the haemorrhagic manifestations of the newborn and prothrombin deficiency, a further investigation has failed to confirm the value of vitamin K administered ante-partum or intra-partum in the prophylaxis of retinal haemorrhages of the newborn, even while vitamin K so administered elevated the prothrombin time of the infant during the period of physiological decline [1320].

See Addendum to this page at end of book.

THE VITAMINS IN RELATION TO DISORDERS OF THE SKIN AND HAIR

TWO ASPECTS require consideration in a discussion of the position of the vitamins in dermatological diseases. The first is that of the manifestations which are attributable to a specific lack of the essential nutrient and the other is the possible therapeutic effect of the vitamin in question upon skin lesions whose aetiology is not or not wholly that of a vitamin deficiency.

Vitamin A

The principal characteristics of deficiency of vitamin A in the histopathological study of the cutaneous lesions are the formation of keratotic plugs in the hair follicles and hyperkeratosis of the surface epithelium; the hyperkeratosis succeeds the initial atrophy of the normal epithelium. The epithelium of the hair follicles undergoes keratinizing changes, and the accumulation of these keratinized cells blocks the hair follicle, forming a keratotic plug through which a broken hair may protrude or the unerupted hair be buried under the mass of abnormal cells. At a later stage the plug may separate and a small crater-like depression remain, the hair being no longer in evidence. Hyperkeratinization of the intervening skin is most marked in the parts immediately around the papules. A moderate lymphocytic infiltration can be discerned in the damaged follicles. Frazier and Hu [1321] noted that the cutaneous changes were most frequent after the age of fifteen. The earliest clinical changes are dryness and roughness of the skin and at a later phase the dry papules appear at the pilo-sebaceous orifices. The papules are conical and may first be appreciated by touch, giving the sensation of 'gooseflesh' to the examining fingers. Variation in size of the papules depends on the duration of the deficiency and in the developed stage they may measure several millimetres in diameter. The surface of the papules may become flattened in the advanced stages, and with subsequent detachment of the mass of keratinized cells there appear the crater-like abnormalities. Dryness is attributable to impairment or loss of function of the sebaceous and sweat glands. Itching is not a common event and infection of the papules is rare. The papules may present no change in colour from that of the unaffected skin but usually develop a brownish hue. Frazier and Hu pointed out that the condition first develops in a localized area and there follows a

rapid symmetrical involvement of the antero-lateral aspects of the thighs or posterolateral areas of the upper parts of the forearm. Other parts of the limbs and body are next implicated but the hands and feet are spared; the scalp tends to escape, except that it may become scaly and that the hair may be dry and fall out. Changes in the nails such as brittleness and transverse ridging have also been reported. Increase of the normal skin markings is a feature in the earlier course of the cutaneous changes while in the markedly deficient subject generalized ichthyosis sparing the palms and soles may develop [1322]. Numerous names have been applied to this form of dermatological picture and among them are phrynoderma, toad skin, and ichthyosis follicularis. Differences of opinion have arisen regarding the specificity of vitamin-A deficiency in the production of the above dermatological syndrome. The vitamin is absent from the epidermis even after large doses of vitamin A have been administered [1333] Stannus [1334] regards phrynoderma as identical with keratosis pilaris which is a disease of the follicles in which horny accumulations develop; he is unable to dogmatize on the nature of the pathogenesis, but considers it questionable whether a vitamin-A deficiency can be regarded as the specific cause although it may under certain circumstances be a factor in its causation. Stannus is of the opinion that the condition is a disturbance in the normal metabolism of the predisposed skin; the disturbance may be partly traumatic in origin and/or partly of nutritional origin, vitamins A, B, and E, and fatty acids being included in the list of possible deficient factors. That essential nutrients other than vitamin A may be concerned is supported by the experimental findings in animals of Sullivan and Evans [1335] who observed that the manifestations of vitamin-A deficiency could be delayed by increasing the amount of vitamin-B complex in the diet, whereas intensification of the deficiency signs followed a deficiency of the vitamin-B complex as well as a deficiency of fat. Wolbach and Bessey [1336] suggested a relationship to riboflavin deficiency and Platt and Lu [1337] postulated an association with the vitamin-B complex. Stannus criticizes conclusions drawn from reported therapeutic results on phrynoderma with vitamin A since, by many, cod-liver oil has been inferred to be synonymous with vitamin A and since other supplements to the diet have often been made at the same time The slow response of phrynoderma to vitamin-A therapy and the need for large doses are generally appreciated (*see* p. 282).

Vitamin-A Therapy in Dermatology

Darier's disease (keratosis follicularis) was found by Peck *et al.* [1338

chilblains [1367]. The assessment of thiamin therapy in these and other cutaneous affections must await further controlled observations.

The Vitamin-B Complex

Reference has already been made to the cutaneous and oral signs of ariboflavinosis and the dermatological lesions of pellagra have been described. A peculiar 'crazy-pavement' type of appear- ance has been reported by Trowell [1368] in the skin of the subjects of 'kwashiorkor'; the lesions first develop on the surface of the buttocks and over the areas of pressure on the back and in the perinaeum and Trowell states that the appearance is as i black paint had been painted on the skin, had dried and cracked and was starting to peel off. The skin exposed by the desquamatio is blanched. Ulceration is a possible complication.

Nicotinic acid has been reported as a satisfactory means treating certain skin diseases, but additional work is required befo the claims can be established. Lynch [1369] noted improveme in some cases of acne vulgaris and remarked on the striki influence of nicotinic acid upon the seborrhoeic condition in a instances. Mashkieleison *et al.* [1349] observed that ribofla 5 mg. t.d.s. for one to four weeks, effected relief of seborrh dermatitis; gratifying results were also procured in rosacea the condition only cleared up when nicotinic acid was prescribed. These authors concluded that the greatest therap effect was to ameliorate the pruritus of lichen planus and ec Lupus erythematosus has been treated by oral and pare administration of nicotinic acid. Relief of the subjective sens [1370] and of the local changes [1371] has been recorded in cases. Birhauser [1372] found nicotinic-acid therapy, prefera the parenteral route, useful in the management of chilblai Calvert [1373] observed rapid regression of the condition fo the intake of 100 mg. nicotinic acid and 3 mg. vitamin B daily. Denton [1374, 1375] advanced the view that nicoti is necessary for the maintenance of normal water balanc skin and of the structure of the collagenous fibrils of the l membrane; when the latter is affected the epitheliu reparative proliferation, dyskeratosis, atrophy and cicatrization.

Pantothenic-acid deficiency in animals is associa striking abnormalities of the skin and hair. The app these findings to man is unwarranted and human ex have yielded negative results [1376, 1377]. A similar would appear to be indicated regarding pyridoxine

See Addendum to this page at end of book

states in the human as contrasted with the animal organism. The position of para-aminobenzoic acid and inositol with reference to the hair is dealt with on p. 286 and the dermatological effects of biotin deficiency have been discussed on p. 49.

Pyridoxine exhibited to some cases of acne vulgaris was stated to be advantageous [1378]; an important feature of this investigation was the marked reduction in the oiliness of the skin, almost to the point of dryness and scaliness, irrespective of the effect on the acne. Wright *et al.* [1379] reported definite improvement following pyridoxine administration in some cases of seborrhoeic or seborrhoeoid eruptions. Wright [1380] was also able to demonstrate the relief of various types of eczema particularly the seborrhoeic variety in some instances by the use of intravenous or subcutaneous administration of pyridoxine. The possible importance of pyridoxine for the maintenance of a normal state of the angles of the mouth is raised by Smith and Martin [1381] Stillans [1382] treated 27 cases of acne vulgaris with 50 mg. pyridoxine daily for three months or more with no demonstrable effect; 2 cases of rosacea on this routine showed gratifying improvement.

Procaine, a derivative of para-aminobenzoic acid, selectively absorbs the rays which produce erythema and sunburn of the skin [1383]. An ointment which incorporated para-aminobenzoic acid proved effective against sunburn [1384]. Para-aminobenzoic acid has been suggested for the restoration of pigmentation in vitiligo, but this view has not been upheld by such studies as those of Benhauer [1385] who treated 41 cases with 100 mg. thrice daily without response. Hathaway [1386], however, reported good results in vitiligo from treatment with the vitamin-B complex. Vorhaus *et al.* [1387] reported 2 cases of pruritic, scaly eruptions which were benefited by treatment with 1 gram of inositol daily.

Concentrates of the vitamin-B complex have been employed in the treatment of a number of dermatological conditions. Kristensen and Vandel [1388] reported success in eczema by saturation of the patient's tissues with vitamin-B complex. Gross [1389] also noted beneficial effects and considered that pityriasis rubra pilaris was attributable to a vitamin-B-complex deficiency. Sayers [1390] presented the view that seborrhoeic dermatoses were probably the cutaneous manifestations of a deficiency of certain components of the vitamin-B complex and was of the opinion that they could be benefited by a diet rich in vitamin B Burgess [1391] observed a satisfactory effect from the vitamin-B complex in the treatment of acute cases of lichen planus but chronic cases proved more resistant. Harris and Gay [1392] concluded that the vitamin-B complex was a valuable adjunct in the therapy of eczema. Vitamin-B

complex was recommended for the management of dermatoses in which allergic factors are involved [1393]. Weisberg and Rosen [1394] consider erythema exudativum multiforme to have a relationship with avitaminosis B and especially with lack of nicotinamide, and report that best results are forthcoming when the latter is administered in massive doses, parenterally if necessary. A lichenoid eruption appeared among the troops who were taking mepacrine regularly and who were existing on a diet from which fresh foods were largely absent; vitamin-B complex, it was discovered, shortened the time of recovery and the possibility of a vitamin-B-complex deficiency as a secondary factor in its production was advanced [1395].

Vitamin C

Besides the haemorrhages into the skin, vitamin-C deficiency is reflected in cutaneous changes. Follicular hyperkeratosis was found to develop in man under experimental vitamin-C-deficient diets; the lesions appeared after 134 days and were first evident on the buttocks and posterior aspects of the calves [1396]. Scheer and Keil [1397] noted that the keratosis was associated with involvement of the perifollicular capillaries; while they could not always be detected clinically, perifollicular haemorrhages could be induced by the application of pressure by a tourniquet. This hyperkeratosis follicularis is indistinguishable from that associated with vitamin-A deficiency but is attributable to lack of vitamin C and can be cured with ascorbic acid.

Vitamin C has been considered to possess a definite relationship with pigmentation of the skin. Ascorbic acid interferes with the formation of melanin [1398, 1399]. Diminution of pigmentation in patients with Addison's disease has been noted although doses far beyond the normal human requirement were necessary [1400, 1401]. Other forms of pigmentation, including chloasma, have also been observed to respond to ascorbic acid [1402]. Increased pigmentation is sometimes seen in scorbutic patients.

Vitamin C has been used in such skin conditions as eczema, impetigo, psoriasis and erythema multiforme but with little or no benefit [1403]. LeWinn and Urbach [1404] treated 18 patients suffering from psoriasis with ascorbic acid and a low potassium diet but could distinguish no beneficial response. From a study of the blood-vitamin C in 181 patients affected with a diversity of skin lesions, Lever and Talbott [1405] could find no indication of a vitamin-C-deficiency state as a factor in the evolvement of these conditions. The position of vitamin C in the prevention and treatment of hypersensitivity to the heavy metals, organic arsenicals

and sulphonamides is not clear since contradictory reports are available.

Vitamin D

It is an interesting fact that although vitamin-D deficiency is not accompanied by any specific skin lesions, the vitamin has been extensively used in the treatment of several dermatological diseases with apparent success. Large doses are administered and the usual precautions should be taken to offset the development of toxic disturbances.

Lever and Talbott [1406] recorded a favourable result from massive vitamin-D therapy in some cases of pemphigus vulgaris acutus, pemphigus vegetans and pemphigus vegetans chronicus, but Eller and Diaz [1407] could discover no value accruing from this therapeutic measure. Psoriasis has been noted to respond to large doses of vitamin D continued for several months [1408] but Huriez and Leborgne [1409] found that only in 10 out of 40 cases was the response good and that in no case was it possible to obtain complete healing of the skin without local applications. Wright [1410] also considered that the beneficial response was only temporary, although this form of therapy was valuable in pustular psoriasis. Acne vulgaris is but temporarily improved with massive vitamin-D therapy [1411]. Encouraging results have ensued from the treatment of scleroderma with very high doses of vitamin D – 200,000 to 300,000 units daily – continued over a year or more [1412, 1413]

Charpy [1414] and Dowling and Thomas [1415] introduced the use of massive doses of vitamin D_2 in the treatment of lupus vulgaris. The method employed by Charpy [1416] is the administration of doses of 600,000 units of vitamin D_2 in alcoholic solution in the following manner. 3 doses are given in the first week, 2 doses per week in the three succeeding weeks and one dose per week during the succeeding months Treatment is continued for about one year. Lupus erythematosus was not benefited. Charpy encountered few toxic symptoms; these included digestive disturbances, dental caries and renal disorder. In his experience Charpy reported that he had never seen a raised blood calcium which had not previously given warning signs such as nausea, vomiting, wasting and depression. The importance of consuming adequate quantities of milk coincident with the calciferol therapy is stressed by Charpy Dowling and Thomas [1417] use calciferol in the form of Ostelin high-potency tablets, each tablet containing 50,000 I.U The dose generally employed was 150,000 units daily, being usually the highest dose the patient will tolerate without the

See Addendum to this page at end of book.

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occurrence of nausea. Occasionally this dosage has to be reduced to 100,000 units per day which is not always adequate, while 50,000 units daily are of little use. Over half of the authors' cases were cured and all were improved; they indicate that once the tuberculous condition is inactive it is worthless to persist with therapy in the hope of resolving the residual lesions. Gaumond and Grandbois [1418] record the remarkable response of a case of extensive lupus vulgaris which had been in existence for twenty-nine years. In the series of Mayer *et al.* [1419] the Charpy method alone did not suffice and most of the patients were given other therapy in addition. Other forms of cutaneous tuberculosis, such as lichen scrofulosum and papulonecrotic tuberculides, were found by Huriez and Leborgne [1420] to respond in similar manner as lupus vulgaris. The possibility of toxic reactions is stressed by Dowling [1421] and Bicknell [1422] considers that these should not be a contra-indication to the treatment in the absence of a pre-existing renal or vascular abnormality; he recognizes acute tenderness of the scalp in the occipital region, a feeling of well-being and increased appetite, soon changing to general fatigue with headache and nausea, polyuria, pains in the teeth, jaws and joints and paraesthesias as among the early symptoms of poisoning. Bicknell suggests that small doses of yeast may abolish minor symptoms and that, when treatment is prohibited, local application of vitamin D_2 ointment may prove of value. The mechanism whereby calciferol operates is not yet apparent but Raab [1423] claims to have demonstrated the bactericidal action of calciferol towards the tubercle bacillus both *in vitro* and *in vivo;* this work requires confirmation.

Vitamin K

The haemorrhagic phenomena of vitamin-K deficiency may be manifested in the skin. Black [1424] discovered a diminished level of prothrombin in 65 per cent of patients with chronic urticaria. Treatment was carried out with synthetic vitamin K by oral administration and relief was obtained in more than 60 per cent of cases. The duration of treatment varied from one to four weeks and relapses occurred in one-third of the subjects but were again relieved by vitamin-K therapy. A beneficial response was more frequently obtained in those demonstrating a prolongation of the prothrombin time. Vitamin K has been suggested for the treatment of purpura [1425].

Vitamin P

Several reports have appeared regarding the use of vitamin P in

dermatology. Purpura of varying origin has responded to vitamin P according to Kuggelmas [1426]. Others have also reported a good effect in purpura [1427, 1428] and Gorrie [1429] recommended its use in the purpuric states occasioned by arsenical treatment.

Essential Fatty Acids

Von Groar [1430] maintained two infants on a diet very low in fat content. Slow growth resulted but a respiratory infection was held to account for this; a generalized eczema appeared in one infant. Holt *et al.* [1431] found that one of three infants fed a fat-free diet developed eczema which was cured when fat was added to the diet. A child suffering from chylous ascites was given a very low fat diet from the age of 3 weeks to the age of 23 months [1432]; the growth response was not impaired but the child seemed susceptible to respiratory infections and on two occasions impetigo appeared proving more resistant to treatment than is usual; at about 8 months of age, a prickly heat eruption developed and persisted for months, and eczematous areas broke out but rapidly yielded to treatment with tar ointment. Over a period of six months an adult was maintained on a diet which was proved to be capable of producing the fat-deficiency syndrome in rats [1433]; no untoward subjective effects were experienced and indeed the individual showed a marked absence of fatigue, but he lost weight and a slight increase in the respiratory quotient – similar to that noted in rats – was demonstrable. Hansen and Burr [1434] indicate that while no specific clinical syndrome is evident on low fat diets during a period of one to two years, these periods are relatively short when compared with animal experimentation and correspond to only about one-third of the time required to produce a deficiency in animals.

On account of the similarity between the dermatological lesions of the experimental animals and infantile eczema the inclusion of fat in the diet was adopted as a therapeutic measure. Hansen [1435] observed that diets rich in fats containing linoleic and arachidonic acids produced significant improvement in a considerable proportion of cases. Similar results have been obtained by other investigators but negative effects have been reported by Epstein and Glick [1436] and Taub and Zakon [1437] Hansen and Burr [1434] draw attention to the occurrence of skin eruptions in the subjects of idiopathic steatorrhoea; these patients present a low fat absorption over long periods and often exist on a low fat diet, medically prescribed, and hence a state of affairs analogous to the fat-deficiency syndrome of rats is obtained These patients were noted to show a very low iodine number of the serum fat. It was found that those

children affected with eczema, who also demonstrated a low i[odine] number, showed the greatest response to the inclusion of fat ri[ch in] linoleic and arachidonic acid in the diet (for example, lard, cor[n oil] and raw linseed oil) and that a rise of the iodine number coinci[ded] with improvement of the skin condition. Hansen *et al.* [14..] observed that more than three-fourths of the infants and more th[an] a half of the adults of a group of 225 cases with eczema had lo[w] iodine numbers for the serum fatty acids. In the majority of the[se] patients addition to the diet of fats rich in unsaturated fatty acid[s] resulted in a favourable clinical response.

The Hair

The pigment of the hair exists in two forms; the soluble form pervades all cells and the other is present as fine granules most numerous in the outer part of the cortex [1439]. The pigment is melanin which is thought to be derived from the action of tyrosinase on tyrosine. Several theories have been propounded to explain greying of the hair; phagocytic action by the cells of the medulla which carry off the pigment, the formulation of bubbles of gas within the hair, and a chemical change in the hair which produces bleaching are among the hypotheses. In view of the experimental evidence in animals of the effect of pantothenic acid and para-aminobenzoic-acid deficiency in the production of greying of the fur, these substances have been suggested for the treatment of grey hair in the human. There is, however, insufficient evidence that the results of animal experimentation are applicable to man and the picture is further complicated by the many possible factors capable of similar action in animals; thus deficiency of iron, copper or manganese may be attended by achromotrichia.

The findings of Brandaleone *et al.* [1440], Kerlan and Herwick [1441], Ralli and Graef [1442] and of Vorhaus *et al.* [1443] would appear to refute any claims for the value of pantothenic acid and para-aminobenzoic acid in the therapy of grey hair. Reports on the efficacy of para-aminobenzoic acid were made by Sieve [1444], Sieve and Ansbacher [1445] and Eller and Diaz [1446]. An investigation of importance with regard to achromotrichia was performed by Frost and Dann [1447] who found that growing dogs receiving thiamine, riboflavin, nicotinamide, pantothenate, pyridoxine and choline developed achromotrichia; inositol aminobenzoic acid or biotin ... effective in preve[nting the] condition whereas liver fract[ion] ... [who]le dried yeast a complete cure.

It is apparent that the esse[ntial] ... factors have been identified, but it is clear ... [a]l deficiency

See Addendum to ...

capable of inducing changes in the texture and colour of the hair. In South Africa severe nutritional deficiency in children may be accompanied by alterations in the hair forming part of the picture of kwashiorkor, or infantile pellagra as Gillman and Gillman [1448] name the condition. The hair of the scalp becomes grey and varying degrees of alopecia ensue. Hughes [1449] found a widespread incidence of achromotrichia in a study of malnutrition in Lagos; the hair was lightly pigmented ranging from white to light yellow or grey and the hairs on the scalp were wavy and not curly as in the normal negro child. Hughes obtained satisfactory pigmentation in the new growth of hair by injections of calcium pantothenate while oral para-aminobenzoic acid was ineffective. Nicholls [1450] observed greying of the hair in children living on a diet which was deficient in many vitamins. Chavarri *et al.* [1451] described disturbances in the hair of children in Costa Rica who suffered from severe avitaminosis; similar changes were not encountered in the hair of adults affected with vitamin-deficiency syndromes. The hair became dry and the colour gradually disappeared. Looseness of the hair may be so marked that a handful of hair can be removed without pain. Spontaneous loss of hair was most pronounced over the frontal area. Loss in colour ranged from slight greying to intense whiteness. All these changes were reversible with an adequate diet alone or together with mixture of vitamin-B complex. The authors were under the impression that the addition of biotin restores the hair to normal at a more rapid rate than ensues with the other forms of therapy. It may be noted here that biotin has no influence on the course of premature baldness.

THE VITAMINS IN RHEUMATIC AFFECTIONS – THE VITAMINS IN SURGERY – THE VITAMINS AND RADIATION SICKNESS – THE VITAMINS AND ALLERGIC CONDITIONS – THE VITAMINS AND CHEMICAL INTOXICATIONS – THE VITAMINS IN AURAL DISORDERS – THE VITAMINS IN DISORDERS OF THE URINARY SYSTEM

VITAMINS IN RHEUMATIC AFFECTIONS

Rheumatic Fever

WHILE NO single essential nutrient has been shown to play a specific rôle in the precipitation of acute rheumatism, studies of the diets of patients affected with this disorder have revealed a frequent inadequacy of vitamin-A consumption. Peete [1452] stresses the importance of adequate amounts of vitamins A and D, protein and milk in the prevention of the onset or recurrence of this malady. A study of the plasma value of vitamin A in acute rheumatism disclosed that it was diminished in proportion to the severity of the disease; the carotene concentration was but little affected [1453]. During the febrile state traces of vitamin A were recoverable from the urine and absorption of vitamin A was impaired.

While Rinehart [1454] suggested that deficiency of vitamin C may operate in the causation of rheumatic fever, it is much more probable that such deficiency is the result of the disease itself [1455]. Diminished urinary excretion of ascorbic acid occurs during the active stage of rheumatic fever but it must also be recalled that, with the administration of salicylates, there is a tendency to an increased elimination of the vitamin in the urine. While it is necessary to correct any hypovitaminosis C and wise to administer amounts of ascorbic acid sufficient to cover the increased demands of the infection, vitamin-C therapy as well as other vitamin therapy does not influence the course of rheumatic fever or reduce the incidence of recurrences [1456]. Rinehart [1457] claimed favourable results from the use of vitamin P.

Salicylates administered either orally or intravenously may produce hypoprothrombinaemia. Salicylates are degradation products of dicoumarol. The use of large doses of salicylates introduced intravenously has been complicated on occasions by haemorrhagic phenomena which may prove fatal. Rheumatic fever is associated with widespread vascular damage which will further enhance any bleeding tendency produced by salicylate

therapy. Fashena and Walker [1458] found that large doses of vitamin K appear to prevent the development of hypoprothrombinaemia and to hasten its restoration to normal levels when the deficiency is already present. According to Shapiro *et al.* [1459] it has been possible to prevent the lowering of the plasma prothrombin induced by 6 grams of acetylsalicylic acid by the administration of 1 mg. of synthetic vitamin K. Owen and Bradford [1460] observed that hypoprothrombinaemia occurred in some degree in all patients treated with massive doses of salicylate, but the depression was more pronounced in some than in others. The lowering of the prothrombin occurred abruptly and was of short duration, returning spontaneously towards normal levels within three days. While the marked depression might take place at any time during treatment from the first to the sixth week, in the majority of cases it was found during the first three weeks of treatment. Owen and Bradford offer the short duration of the hypoprothrombinaemia as an explanation of those reports of the absence of depression of the prothrombin level during salicylate therapy [1461]. Quick [1462] emphasizes that even mild dosage of salicylates may depress the prothrombin level when some other dysfunction exists, whether it be of kidney, liver or other organ. With the common mode of salicylate treatment of rheumatic fever, it would appear that there is not much clinical significance in the lowered blood prothrombin since haemorrhagic phenomena are rare even when salicylate intoxication has been produced. Higley [1463] considers that the routine administration of vitamin K is unwarranted when salicylates are prescribed in daily doses of 150 grains; he denounces some of the reports of haemorrhage of salicylate administration since doses as large as 10–15 grams per day had been maintained over long periods without evidence in haemorrhage. Owen and Bradford conclude that because of the uniformity with which the blood prothrombin returns to normal levels during continued administration of salicylates, hypoprothrombinaemia as a cause of serious haemorrhage in the salicylate-treated patient is an unlikely event; however, when surgical procedures are contemplated, the added risk of haemorrhage warrants the use of vitamin K. Clausen and Jager [1464] state that the prolonged prothrombin time does not appear to be a factor in causing death from salicylate intoxication. The dicoumarol action of salicylates does not explain the transient nature of the prothrombin changes, nor have any liver changes been demonstrated to be attributable to salicylates [1465].

Salicylates and para-aminobenzoic acid appear to have a reciprocal effect in increasing their concentration in the blood when they are administered orally together [1466].

from a mechanical point of view [1483]. Normally the uninjured skin of guinea-pigs contains practically no phosphatase. Two peaks of phosphatase activity are observed after trauma, one corresponding to invasion of the wounds by leucocytes, and the other associated with the differentiation of collagenous fibrous tissue. Phosphatase is connected directly or indirectly with collagen formation. The first peak of the phosphatase activity occurs normally, but the second is absent or very small in vitamin-C-deficiency states [1484]. Epithelialization of the wound may take place fully in acute ascorbic-acid deficiency, but the pattern of the fibroblasts is irregular. The scar tissue of animals and man on a low vitamin-C intake contains less of the vitamin than does normal scar tissue [1485, 1486].

It has long been recognized that there is impairment of wound healing in human subjects affected with scurvy. Taffel and Harvey [1487] suggested that vitamin-C deficiency in man may be one of the major causative factors in delay of wound healing in the absence of infection. Lund and Crandon [1488] found the incidence of post-operative hernia to be highest in patients with low values of vitamin-C reserves. Vitamin C is necessary for the normal fibroblastic activities in the healing of wounds. Surgical procedures probably necessitate an increased requirement of the vitamin. If ascorbic acid be supplied during the post-operative period in the presence of an ascorbic-acid-deficiency state, it may still operate in wound healing. Pre-operative and post-operative administration is indicated in deficiency states, but it is not to be anticipated that minor degrees of vitamin-C deficiency will seriously affect wound healing. Lack of healing may appear in the wounds of individuals manifesting no clinical signs of avitaminosis C, and normal healing ensue only after the vitamin has been prescribed. Vitamin-C nutrition is of particular importance in surgery of the gastro-intestinal tract. Lund [1489] found a prompt fall of the plasma-ascorbic-acid levels following surgical operations, but he considered that the pre-operative value was a more significant indicator of depleted reserves. It is not to be expected that vitamin C in quantities above those necessary to provide ample tissue storage will enhance the healing properties of wounds. However, Ruskin [1490] considers that the local effect of ascorbic acid is valuable as distinct from the systemic level of the vitamin. He advocates vitamin C in local application as an additional aid to healing, and recommends the use of vitamin-C-sulphonamide compounds in the treatment of chronic suppurating wounds following mastoidectomy.

The thiamine concentration of wounds is greater than that of the surrounding normal tissue as studied in mature, healthy female rats; the vitamin B_1 content of the wound is highest at the stage

of most rapid healing [1491]. Vitamin D [1492] and [1493] appear to play no part in wound healing. The liver oil in the healing of wounds is considered elsewhe *al.* [1494] stated that cod-liver oil, coconut oil, pure and liquid paraffin all stimulated collagen formation degrees, but epithelial regeneration was only promoted acid.

Vitamins in Bone Repair

Animal experiments have shown that the vitamins are co in the repair of bone Copp and Greenberg [1495] stud aspect. Vitamin-A-deficient rats showed less callus formati less active calcification than normal rats. Treatment with vita restored these processes to normal levels but untreate demonstrated a significant delay in fracture healing. In ra rats there was little calcification of the callus, while in those rec toxic doses of vitamin D, the callus was small, calcification red and recovery in strength delayed

Much attention has been paid to the influence of ascorbic aci the repair of bone The amount of bone regenerated in an inj area in the guinea-pig is directly proportional to the quantity vitamin C supplied to it up to a maximal level: in conditions of of the vitamin the normal inflammatory reaction of injured tissu imperfect and there is delay in the transformation of fibroblasts osteoblasts [1496]. There is a delayed absorption of the haemator in the fracture [1497] Bourne [1498] states that both endosteu and periosteum play an important part in the regeneration of a injured bone, and that the activity of both is impaired by a deficienc of vitamin C. Vitamin C is considered to be essential for the produc tion of bone salts and for the formation of callus in a fracture. Osteoblastic function is influenced by vitamin C, in the absence of which the osteoblasts are imperfectly formed. This viewpoint is in contrast to what has been propounded by Wolbach and Bessey [313] who considered that ascorbic acid was not concerned in calcifica- tion. The rôle of vitamin C in calcification explains the faulty calcium deposition in the bones of scorbutic patients There is a reduction both of bone and serum phosphatase in scurvy [1499] but Bourne points out that the apparent reduction in phosphatase is probably due to reduction in the amount of bone matrix pro- duced, rather than to a reduction of the phosphatase *per se*. The importance of vitamin-C nutrition in normal healing of fractures is thus evident, and although larger quantities of the vitami be necessary for more extensive injuries, vi not further accelerate heali

Shock

The investigations of Govier, Greer and Greig [1501, 1502, 1503, 1504] have revealed an important relationship between thiamine and shock. Thiamine had a beneficial effect on shock induced in dogs by fractional bleeding. The blood pyruvate level increases in dogs during shock, and it was found that the amount of bleeding required to produce the condition in vitamin-B_1-deficient animals was considerably less than that necessary to produce shock in vitamin-B_1-fortified animals; in the latter group there was a constant tendency for the blood pressure to rise after bleeding, whereas hypotension persisted in the thiamine-deficient animals. A breakdown of cocarboxylase into thiamine occurs in the tissues in shock and, since the latter substance is metabolically inactive, the animals, although well supplied with vitamin B_1, are physiologically deficient. Thiamine diffuses out of the tissues into the plasma in which a rise of the thiamine level appears, while the cocarboxylase concentration in the tissues diminishes. Anoxia leads to a similar effect. Administration of large amounts of thiamine to these animals produces re-synthesis of cocarboxylase. Other co-enzymes such as those containing nicotinamide and riboflavin also suffer a breakdown in the tissues. Hence the administration of large amounts of vitamins in the therapy of shock and anoxia is indicated to counteract the co-enzyme breakdown; a cell deprived of its co-enzymes dies. Andrea *et al.* [1505] discovered a diminished excretion of riboflavin in 23 cases of burns and injuries.

In haemorrhage and haemorrhagic shock in rats and guinea-pigs, the vitamin-C content of the adrenal glands is reduced and is restored during the recovery period; there is no tendency to recovery of the level before death. Alterations in the vitamin-C concentrations of other tissues are thought to be associated with increase of the secretion of the adrenal cortical hormones; vitamin C participates in the formation of the latter [1506]. Diminution in the ascorbic-acid content of the adrenal cortex has been demonstrated in experimental animals following burns [1507]. Ungar [1508] found that ascorbic-acid administration reduced the mortality rate in animals subjected to a standard traumatizing technique. Ascorbic acid was shown to increase resistance to the effects of haemorrhage when administered intravenously [1509]. The investigations of McDevitt and her associates [1510] indicate that animals with a low intake of vitamin C are more susceptible to traumatic shock than those on a normal diet. Repeated trauma in animals with normal vitamin-C intake increases resistance to

traumatic shock, but this effect is not apparent in the same degr in animals with a low vitamin-C intake. A clinical study of th influence of ascorbic acid on traumatic shock was undertaken b Holmes [1511]. There was a considerable decrease of shock whe 500 mg. of vitamin C was taken orally within an hour before operation. This medication was also effective in preventing shock or post-operative weakness secondary to tooth extraction and immediate administration of 500 mg. of vitamin C to 35 patients who had suffered various types of accidents appeared to improve their condition. Excellent results were also claimed from the pre- and post-operative intravenous administration of 500 to 1,000 mg. of ascorbic acid in sterile, buffered solutions

Radiation Sickness

Vitamin B_1 and members of the vitamin-B complex have been used in the treatment and prevention of radiation sickness. Thiamine injections have been reported to exert a favourable effect on the condition [1512, 1513, 1514]. When young rats were exposed to a weak source of gamma radiation they suffered no immediate adverse reaction, but subsequently manifested signs of damage to the generative organs and showed premature aging [1515]. The toxic response to the irradiation could be decreased by the addition of vitamin-B complex to the food [1516] Bean *et al.* [1517] observed that certain of the signs of radiation sickness – nausea, vomiting, cramps, diarrhoea and headache – and the behaviour of the urinary pigments and of codehydrogenases I and II resembled those of severely ill pellagrins In a later study [1518] they noted that individuals who had existed on a diet poor in the vitamin-B complex were more prone to suffer from radiation sickness, and that this could be prevented or reduced in severity by the administration of nicotinic acid or vitamin B_1 for several days prior to the institution of X-ray therapy; it was concluded that the optimum time for vitamin supplementation was before and not after symptoms have appeared. The value of pyridoxine in irradiation sickness would appear to have been confirmed by several reports on this form of treatment Intravenous injection of 25 mg. of pyridoxine was tated to relieve the condition. One injection was usually sufficien ut it may be repeated at intervals of twenty-four to seventy-two ours if necessary [1519]. Scott and Tarleton [1520] recommend e intravenous injection of 25 mg of pyridoxine after each treatent and Van Haltern [1521] advises 25 to 50 mg. of pyridoxine ravenously at intervals of one to four days from the onset of nptoms. Pyridoxine may also prove effective when given by the l route. Fifty mg. in the morning and 25 mg. at noon and in the

evening are suggested by Reeves [1522]. Shovron [1523] pointed out that pyridoxine therapy also raises the leucocyte count.

Allergic Conditions

Nicotinic acid has been employed in the treatment of bronchial asthma. Melton [1524] observed definite improvement in 16 out of 19 cases following intravenous administration of the vitamin, whereas the oral route produced good results in only 5 out of 9 cases, during an acute paroxysm; he reported that when the vitamin is taken orally over a considerable period, the frequency and the severity of the attacks decrease.

Three of seven cases of asthma were rendered worse by nicotinic-acid treatment in the series of Neuwahl [1525]. The initial record of this form of treatment was made by Maisel and Somkin [1526] who claimed relief of the paroxysm and reduced incidence of attacks with intravenous and oral nicotinic-acid administration. Another report [1527] states that nicotinic acid is useful in asthma, spastic bronchitis and urticaria.

Vitamin C has also been exhibited for the treatment of bronchial asthma. Hochwald [1528] found that intravenous injections of large amounts of ascorbic acid relieved an asthmatical attack, but Hunt [1529] was unable to confirm this or to observe any beneficial effect on the incidence of attacks with continued oral intake of vitamin C. The latter author did not observe any reduction in the amount of adrenaline required to relieve the spasm following the use of the vitamin. Other conflicting reports have appeared in the literature on the influence of vitamin-C therapy on bronchial asthma, but it is not established that it is of any definite value.

Vitamin C has been recommended for allergic conditions on the experimental evidence of its ability to prevent anaphylactoid shock in guinea-pigs, and to decrease the toxicity of histamine [1530]. Success has been claimed in the treatment of hay fever with vitamin C [1531, 1532]. Friedlander and Feinberg [1533] were among those who failed to discover any advantage resulting from high dosage of vitamin C and an editorial in the *Journal of the American Medical Association* [1534] expresses the view that vitamin-C therapy for hay fever and other allergic conditions is useless and wasteful. Vitamin D and vitamin E do not appear to be beneficial for allergic states.

Urticarial conditions are considered in the section on dermatology.

DETOXICATION OF ARSENIC, LEAD, ETC.

Guinea-pigs which had been depleted of vitamin C were found to be more readily sensitized to neoarsphenamine when administered

intracutaneously than normal control animals [1535]. When neoarsphenamine and mapharsen are exposed to the air they undergo a change of colour to dark brown and McChesney [1536] indicates that ascorbic acid tends to have its greatest detoxifying effect on the arsenicals which are most susceptible to oxidation *in vitro*. The precise mode of action of vitamin C in this respect is not yet fully understood, but the vitamin does not diminish the efficacy of the arsenicals. Nutritional deficiencies especially of vitamin C and riboflavin augment the susceptibility to aromatic hydrocarbons [1537]. Guinea-pigs in a scorbutic state were seriously affected following an injection of hydrazine, while 30 mg. ascorbic acid daily afforded complete protection [1538]. Not all the experimental evidence has shown a relationship between vitamin C and protection against arsenic, and the clinical reports have also been at variance. It is not possible to dogmatize as to the efficacy of ascorbic acid as a prophylactic or therapeutic agent for the untoward reactions of arsenotherapy. Difficulty in evaluating the use of vitamin C in lead intoxication also exists. Thus, for example, the reports of Holmes *et al.* [1539] of the vitamin proving a most effective detoxifying agent in lead poisoning are offset by the conclusions of Evans *et al.* [1540], who consider that the vitamin possesses little merit in this direction. There also remains considerable doubt regarding the position of vitamin-C therapy in gold, T.N.T., benzene and other intoxications.

Alkaptonuria

Vitamin C may function in the normal metabolism of tyrosine. Sealock and his colleagues [1541] were able to produce alkaptonuria in guinea-pigs maintained on a diet low in the vitamin by the administration of tyrosine or phenylalanine Vitamin-C therapy proves effective in reducing the alkaptonuria in guinea-pigs but is unsuccessful in human alkaptonuria [1542].

DÉAFNESS, OTITIS MEDIA AND MÉNIÈRE'S SYNDROME

Vitamins have proved of little value in the treatment of deafness or otitis media. Experiments in animals demonstrated that a state of vitamin-A deficiency produced bony overgrowth in the auditory tube, and resulting changes in the eighth nerve and structure of the inner and middle ear [1543, 1544] These changes, however, do not appear to occur in the human subject. Hughson and Thomson [1545] conclude that vitamins have proved most dis-

appointing in the therapy of deafness and that the experimental findings of animals bear no significant relationship to human clinical deafness. Vitamin B_1 has been prescribed for tinnitus and for deafness. While there are reports of improvement following its use, the prevailing view is that these studies have been inadequately controlled, and that thiamine is not a practical measure for the relief of these conditions. A similar conclusion appears to apply to nicotinic acid. Deficiency of ascorbic acid in animals may lead to changes in the articulations of the ossicles, thickening of the submucosa of the middle ear and haemorrhage. In human scurvy bleeding into a part of the auditory apparatus may complicate the disorder, but there is no evidence of other damaging effects of a deficiency of ascorbic acid in this system. Rats maintained on a diet inadequate in vitamin D may demonstrate demyelinization of the cochlear nerve and the frequent incidence of otitis media, the latter being also encountered with a vitamin-E-deficiency diet which may in addition be associated with fibrous replacement of the muscles of the middle ear [1546]. Wallner [1547] concluded that vitamin D was not concerned in the aetiology of otosclerosis and that its administration did not retard its progress. Vitamin-E therapy likewise is probably valueless in otosclerosis and deafness.

Nicotinic-acid therapy has yielded good results in Ménière's syndrome. A combination of thiamine chloride and nicotinic acid was employed by Harris and Moore [1548]; 10 mg. of the former were administered twice daily and 50 mg. of the latter five times a day, raw red ground meat, liver, wheat germ, vegetables and fruit being also included in the diet. These observers noted a gradual recovery in 17 out of 20 patients, the remaining 3 showing improvement in hearing and tinnitus. Considerable work on this aspect has been conducted by Atkinson [1549, 1550, 1551]. By means of the patient's reaction to an intradermal injection of histamine he divides the subjects of this disorder into a histamine-sensitive and a histamine-insensitive group. The latter group are benefited by the use of vasodilator drugs and nicotinic acid is employed for this purpose. An intramuscular injection of 30 mg. of nicotinic acid is administered, and if no untoward effects ensue, this is followed by an intravenous injection of a similar dose, which is repeated daily or on alternate days for six to eight doses. With each intravenous injection the dose is increased by 5 mg. to the limit of tolerance. Oral treatment is instituted a few days after the commencement of the injections, 50 mg. being prescribed twice or thrice daily. At the cessation of the intravenous injections, the intramuscular route is adopted, and an injection is given daily for several months, the frequency of the injection being gradually reduced. Thereafter nicotinic-acid administration is continued by

the oral route alone. Atkinson states that the benefits accruing from this type of treatment are superior to any of the other medical methods at present in vogue. Williams [1552] found that nicotinic acid is not so effective when given by mouth as when given hypodermically. He administers the compound by hypodermic injection, starting with 25 mg. daily and increasing by 25 mg. daily until an optimum dose, usually 100 mg. daily, is being administered. This amount is continued for a month or more, and then oral medication is tried, 100 mg. twice daily usually being necessary. In addition to the nicotinic-acid therapy the patient is instructed to reduce his fluid and salt intake and potassium nitrate is prescribed. He obtained satisfactory results in 50 out of 62 cases.

THE VITAMINS IN DISORDERS OF THE URINARY SYSTEM

The association of a deficiency of vitamin A and the production of urolithiasis in animals has long been appreciated. The metaplastic epithelial changes offer a focus for the development of renal calculi. However, deficiency of vitamin A in animals has frequently failed to result in stone formation and urinary stones may be found in cattle and sheep receiving an abundance of the vitamin from green pasturage [1553] There is little evidence to suggest that a similar process operates in the genesis of renal calculi in the human subject. Twenty patients suffering from urolithiasis were examined for the rate of dark adaptation and for the vitamin-A content of the blood and Jewet, Sloan and Strong [1554] were unable to discover an difference in the results as compared with a group of normal co trols. In addition, these investigators did not find epithelial hyp plasia characteristic of vitamin-A deficiency in the post-mort examination of the respiratory or urinary tracts of 78 subj affected with urolithiasis Deficiency of vitamin A in childhoo rarely accompanied by calculus formation.

Vitamin A appears to bear a relationship to renal functio the vitamin-A-deficient rat and dog there occurs a decrease urea clearance, whereas large doses of the vitamin effe increased urea clearance which is apparently attributa increased glomerular filtration [1555] Herrin [1556] rep rise in the urea clearance in 11 of 13 human subjects fo doses of 50,000 to 75,000 I.U of vitamin A daily. This effe the animal, is of temporary nature and is not sustained. I renal function in chronic nephritis was considered to medication with high dosage of vitamin A and with bile sa

Very high values of the blood concentration of vitam been observed in chronic nephritis. Bauman

colleagues [1558] state that certain conditions which deplete the liver of its protein stores may also interfere with liver storage of the vitamin. A further factor which is postulated as participating in the production of the raised vitamin-A level is the elevated blood-fat content. The response of the plasma-vitamin-A level following intake of 75,000 I.U. of the vitamin was found to be much more marked and the elevation more prolonged in the subjects of renal disease as compared with a group of normal controls [1559]. Even when a high vitamin-A concentration is found in the blood in chronic renal disease there is usually a low reserve of the vitamin in the tissues. The normal kidney does not excrete vitamin A but in impaired renal function the vitamin may appear in the urine. This loss probably combines with a defect in the absorption or metabolism of the vitamin in the causation of the depleted tissue stores. The carotene value in the blood is high in nephrotic conditions, being associated with the increased blood-fat level.

Other aspects of the influence of vitamin nutrition on renal function are largely referable to animal experimentation and are mentioned elsewhere in the text, as is the renal damage which may ensue during treatment with massive doses of vitamin D, and the diuretic action of vitamin C. Thiamine has been considered to possess diuretic properties; it was possible in the fasting rabbit to double the urinary excretion, after the administration of 100 c.c. of water, by the injection of 0·1 mg. per kg. of the vitamin [1560]. Shute was impressed with the value of vitamin E in preventing gross evidence of impaired renal function when prescribed during pregnancy. He treated 13 women, who demonstrated evidence of chronic nephritis or impaired renal function, with 25 mg. of synthetic alpha-tocopherol daily, and obtained improvement in 10; this improvement appeared to be limited to the tubular system of the kidney, and although improvement developed rapidly it was transient unless the treatment was continued [1561]. Shute also claimed that 3 cases of acute nephritis appeared to have benefited rapidly by the administration of large doses of vitamin E [1562].

THE VITAMINS AND PHYSICAL FITNESS

AN ERRONEOUS conception exists in the minds of many of the public as to the 'tonic' effects of vitamins and this has in no small measure been fostered by the shrewd advertising adopted by some pharmaceutical companies. The postulation of false claims has done much to discredit the true value of vitamin therapy among the medical profession It is necessary to consider first the influence of exercise on the vitamin requirements of the body, and secondly whether a beneficial action will accrue from the administration of vitamins on the capacity for physical exertion in individuals not suffering from a vitamin-deficiency state.

Vitamin Requirements in Relation to Exertion

There is little evidence that increased physical activities necessitate increased requirements of vitamin A and the Food and Nutrition Board of the National Research Council of the United States (1948) does not modify its suggested daily allowances for man in proportion to exertion. Guilbert *et al.* [1563] state that for all animals including man, energy expenditure does not affect the vitamin A or carotene requirements and subsequent work has confirmed this view, and has based the estimation of the need for vitamin A and its provitamins on the body-weight.

The minimal adequate allowances of thiamine, riboflavin and nicotinic acid are modified by the energy output increasing with the activity of the individual. Holt [1564] observed that while exercise increases the caloric intake, the absolute requirement of thiamine does not demand any increase in the proportion of thiamine per calorie The conclusion arrived at by the Food and Nutrition Board of the National Research Council of the United States (1948) was that the proportion of vitamin B_1 required decreases as the calories increase above the lower levels.

Contradictory reports have appeared regarding the requirements of vitamin C in those performing work of a strenuous nature, but no increased allowances are offered by the Food and Nutrition Board for moderately or very active individuals. A similar conclusion is reached regarding vitamin D. Vitamin E would appear to play no part in the neuromuscular functions of normal man, and the minimal human requirements are as yet unknown.

The Effect of Vitamin Supplements on the Physical and Mental Capacity

Any investigation on physical capacity and the response to supplements of vitamins must take cognizance of the increased minimal requirements of certain vitamins during hard physical exertion.

Human subjects showed no diminution in their capacity for physical work following the consumption of a diet markedly deficient in vitamin A over a period of six months [1565] and dogs profoundly depleted of their reserves of vitamin A revealed no evidence of decreased bodily activity [1566].

Kaiser [1567] disproved the claim that isolated muscle, perfused with thiamine, showed an increased response to acetylcholine. Barborka *et al.* [1568] found significant differences in 'double work' performances of subjects who had existed on reduced thiamine, riboflavin and ascorbic acid intakes, during a period of twelve weeks. Reduction in physical ability was observed in nicotinic-acid deficiency [1569]. Keys *et al.* [1570] criticized the methods of elucidation of the effects on work performance of normal individuals, who have performed very hard work while subsisting on a diet severely restricted in the vitamins of the B complex. They were unable in their own controlled studies to corroborate any claim to a reduction in work capacity under conditions of even greater vitamin restriction over even longer periods than those of former experiments. They stated that while it was true that increased physical exertion demands an increased intake of vitamin B, this was guaranteed by simply increasing the total amount of food consumed. No alteration of capacity for brief extreme exercise or prolonged severe exercise was noted by Keys and Henschel [1571] following the administration of large daily supplements of thiamine chloride, riboflavin, nicotinic acid, pyridoxine, pantothenic acid or ascorbic acid over periods of four to six weeks. Supplements of vitamins A, B_1, C and D, riboflavin and nicotinamide to factory workers did not produce any effect on their output of material [1572]. After a year's administration of a supplement approximating to half the daily requirements of vitamins A, B_1, C and D, no effect was witnessed in a group of children on the height, weight, strength of grip, haemoglobin, dark adaptation, resting pulse rate, vital capacity and endurance as measured by the R.A.F. mercury test [1573]. Thiamine, cocarboxylase, riboflavin or vitamin-B complex administered intravenously following a period of exertion produced no influence on recovery from muscular fatigue in human subjects receiving an adequate diet [1574]. In girls, Fowke [1575] was unable to establish any significant physical differences due to

consumption of additional supplies of vitamins A, B and C. On the other hand, Borsook [1576] reports that supplements of vitamins A, C, D and B_1, riboflavin, nicotinamide and calcium carbonate, given to aircraft workers, while showing no significant influence on absenteeism in the first six months, resulted in a reduction of 18·6 per cent absenteeism in the second six months, as compared with a control group receiving placebos; superior performance was also noted in the group receiving vitamins. Borsook is of the opinion that a long period is necessary before the effects on performance are manifested. The Council of Food and Nutrition and the Council on Industrial Health in the United States [1577] concluded that the indiscriminate administration of vitamins to industrial workers is irrational from a therapeutic aspect, unwise from a nutritional point of view and uneconomical.

The work of Crandon *et al.* [1578, 1579] has revealed that man can tolerate extreme deficiency of ascorbic acid for a long time without the development of any reduction in physical capacity. While undoubtedly scorbutic states will reduce the work endurance times, it does not appear that vitamin-C administration to men consuming an average normal diet will effect a greater tolerance to exercise. Harper *et al.* [1580] found an increase in vital capacity and in breath-holding and endurance times in cadets receiving supplements of vitamins A, C and D over a period of five months, as compared with a control group. There are certain possible criticisms of these conclusions which were recognized by the investigators, and Jenkins and Yudkin [1581] noted no effects on vital capacity, breath-holding and endurance tests and the fasting pulse rate in a group of children receiving a supplement of vitamins A, B_1, C and D. Johnson *et al.* [1582] found, that if the previous diet had been satisfactory, deprivation of vitamin C for two months did not produce in manual workers any detectable deterioration in the day's work; supplements of 75 mg vitamin C daily were of no detectable benefit to manual workers over a period of two months with respect to physical vigour for hard work or efficiency in the day's work. Keys [1583] sums up the situation of the relationship of food to physical exercise; while there is little doubt that physical performance is hindered when real deficiencies exist, no conclusive statement can be made as to dietary means of increasing the performance of those not clearly malnourished.

Influence of Excessive Perspiration and Hot Climates on Vitamin Requirements

At this point it is useful to consider the loss of vitamins in the sweat and the influence of hot environments on the vitamin requirements.

Tennent and Sibler [1584] determined the excretion of ascorbic acid, thiamine, riboflavin and pantothenic acid in both thermal sweat and sweat induced by exercise. No ascorbic acid was found and the average loss of dehydro-ascorbic acid was 0·23 mg. per hour; insignificant amounts of thiamine were excreted and the average hourly loss of riboflavin and pantothenic acid were respectively 10 and 25 micrograms. Similar results were found by Cornbleet and his co-workers [1585] who estimated values of 150 micrograms of thiamine per litre of sweat, 120 micrograms of riboflavin, 300 micrograms of pantothenic acid and 200 micrograms of nicotinic acid. Sargent *et al.* [1586] concluded that the loss of water-soluble vitamins from the sweat with the possible exception of nicotinic acid is insignificant. The vitamin-B_1 requirements for the growth of rats exposed to a tropical environment are not greater and may be less than those of temperate conditions [1587].

Additional vitamin B did not improve the human capacity for hard work in conditions of extreme heat up to periods of one week [1588]. Johnson [1589] concluded that the vitamin requirements for the avoidance of deficiency syndromes are the same in hot climates as in cooler conditions. It is pointed out by Keys [1583] that the unconscious economy of effort which occurs in hot weather may more than compensate for the small amounts of vitamins lost in the sweat. Kark *et al.* [1590] concluded that high vitamin intakes for a healthy adult population residing in the tropics are of no benefit. There does not appear to be any difference between the vitamin requirements of individuals living in tropical or in temperate climates; nor is there any improvement in the capacity for work performed at high temperatures, following the addition of vitamin supplements to the diet.

Tolerance to Cold

Man's tolerance to cold has also been investigated with regard to the possibility of acquiring an increased resistance to its damaging effects. It was found that supplements of vitamins B_1 and C, riboflavin and nicotinic acid were not attended by any effects on mental functions or on the rectal and skin temperatures [1591].

SOME ASPECTS OF VITAMINS IN RELATION TO INFECTION

Vitamin A

THE POSITION of the vitamins in relation to resistance to infection has been confused by failure to distinguish between the specific and non-specific effects of a deficiency of an essential nutrient. An erroneous conception arose regarding the properties of vitamin A in this direction and the term 'anti-infective' was applied to the vitamin. The primary lesion of vitamin-A deficiency is a metaplastic change in the epithelial structures, the epithelial cells being transformed into a squamous, keratinizing variety. This alteration in cellular structure provides conditions which are favourable to bacterial multiplication The bacteria concerned are, under normal conditions, purely saprophytic in character and in the altered local morphology they become capable of producing local inflammatory changes with little if any tendency to systemic infection. This breakdown in the 'first line of defence' will be repaired by vitamin-A therapy and it is only in conditions of vitamin-A deficiency that treatment with the vitamin can be expected to prove of value. The recommendation of vitamin-A therapy in numerous types of infections has formerly been made, but, in the absence of a specific lack of this substance in the tissues, this form of treatment cannot be expected to afford satisfactory results. Experiments with vitamin A as a possible prophylactic agent for the common cold resulted almost uniformly in negative results, and the supplementation of the diet of infants with the vitamin produced no beneficial response on the incidence or severity of respiratory infections [1592]. Hess [1593] concluded that vitamins A and D did not increase the immunity to respiratory infections, whereas lack of vitamin C might cause heightened susceptibility to infection of the respiratory tract. Cowan *et al.* [1594] were unable to observe any beneficial action of vitamin A in the prevention of the common cold No correlation between vitamin-A intake by the mother and the incidence of puerperal infection was discovered [1595]. Studies in animals have revealed no evidence of defect in leucocyte or antibody production in states of vitamin-A deficiency.

A sharp fall in the vitamin-A concentration of the blood appears following the onset of an acute infection Josephs [1596] found that the vitamin A, carotene and total lipides of the serum were reduced in pneumonia, but that in convalescence there occurred

a rise of the serum lipides well above normal, and that in general the curve of the blood-vitamin-A level paralleled that of the lipides; under the age of 2, however, vitamin-A supplements were necessary to produce a rise similar to that seen in the older children, and under 8 months of age there was little or no tendency towards an elevation of the blood-vitamin-A levels. Clausen and McCoord [1597] had previously demonstrated that febrile illness was associated with a rise of plasma-vitamin A during convalescence, and that a similar rise could be determined one to two days after artificial pyrexia. An explanation which was put forward for the decreased plasma-vitamin A observed during the course of an infection was that of increased temporary demands and also an enhanced destruction of the vitamin. Popper and Steigmann [1598] suggested that the hepatic changes which develop inhibit the release of the vitamin from the liver into the blood. This view is supported by the findings of Ellison and Moore [1599] who observed that the hepatic stores of vitamin A were not reduced in death from acute infectious processes. Defective absorption of the vitamin from the intestinal tract probably also participates in the production of the low blood-vitamin-A concentration. The high values during convalescence may be due to improved intestinal absorption associated with a temporary delay in the capacity of the liver to store the vitamin.

Chronic infections deplete the body stores of vitamin A and the amounts present in the liver may be considerably reduced. Infection, even without fever or gastro-intestinal disturbance, may greatly diminish the absorption of vitamin A or carotene [1600]. Beese *et al.* [1601], in a study of 29 patients affected with pulmonary tuberculosis, observed that absorption of vitamin A was poorer in this group than in normal individuals and suggested a more liberal intake in such patients. The level of vitamin A in the plasma of tuberculous subjects is lowered in proportion to the extent of the disease; the vitamin-C level may be greatly reduced in the advanced stages [1602]. Raab [1603] reported beneficial effects from the application of an ointment containing vitamins A and D to the skin over the site of a tuberculous gland which had been incised and drained.

Thiamine and the Vitamin-B Complex

Vitamin B_1 has not been shown to possess any activity in the prevention of post-diphtheritic paralysis or in its treatment; the cardiovascular complications are also unaffected but a sense of well-being and increased appetite are said to accompany the administration of thiamine in the convalescent stage [1604].

Laboratory reports on the effects of vitamin-B deficiency in induced pneumococcal infections in animals have been inconsistent. Rats deficient in thiamine show an increased susceptibility to leprosy [1605].

A considerable amount of work has been conducted on the influence of vitamin B on the susceptibility of the organism to virus disease. Foster *et al.* [1606] reported that mice maintained on a vitamin-B_1-deficiency diet were protected to a greater extent against the lethal effects of intracerebral injection of a suspension of the poliomyelitis virus than were mice receiving an adequate supply of the vitamin. In a subsequent study they found that dietary deficiency of thiamine or partial starvation of animals on a complete diet were similarly effective, but the latter to a lesser degree [1607]. These results were confirmed by Ramussen *et al.* [1608] for mice injected with the Lansing strain of poliomyelitis or Theiler's encephalomyelitis virus. Thiamine deficiency did not materially alter the susceptibility of monkeys to poliomyelitis [1609]. Weaver *et al.* [1610], however, obtained no evidence that deficiency of the vitamin-B complex or partial inanition had any effect on susceptibility to poliomyelitis and Ramussen *et al.* [1611] obtained similar negative results for riboflavin deficiency.

The beneficial action of thiamine deficiency in poliomyelitis was evidenced by a decreased incidence of paralysis, reduction in mortality rate and by prolongation of the incubation period. When the observation of the animals was extended, it was observed that what was a marked difference in the paralytic and mortality figures at the fifteenth day after inoculation was insignificant when examination was conducted on the twenty-eighth day. The most pronounced resultant of the hypovitaminosis was a prolongation of the incubation period. Sprunt [1612] offers some explanation of the malnutritional immunity According to Olitsky and Schlesinger [1613] the rate of intradermal spread of virus varies inversely with the quantity of interstitial fluid. Sprunt noted that the resistance of rabbits to virus infection could be increased tenfold with prolonged starvation, providing the animal had free access to drinking water He used the vaccinia virus which he injected intradermally. The failure of virus to spread normally in the starved animals is due to the increase in the amount of interstitial fluid which occurs when the animals are allowed to drink as much as they desire. When fluid restriction is imposed on the starved animal, the spread proceeds at the normal rate and the increase in virus resistance disappears.

Ward *et al.* [1614] investigated the possibility that the level of thiamine or nicotinic acid in the diet might determine whether poliomyelitis resulted in paralysis or non-paralytic phenomena;

negative results were obtained. The amount of riboflavin, pantothenic acid and biotin excreted in the urine in 10 patients with poliomyelitis was within the normal range [1615]. McCormick [1616] stated that the diets of patients with infantile paralysis was often low in vitamin B_1 and he reported good results following the administration of large quantities of the vitamin. Stone [1617] considered that treatment with vitamins A and E and with artificial fever was of value in poliomyelitis.

A high proportion of patients with active pulmonary tuberculosis was observed to show signs of nicotinic acid and riboflavin deficiency [1618]. Oral administration of penicillin may produce a state of nicotinic-acid deficiency [1619]. Pyridoxine deficiency in rats is associated with a profound reduction in specific antibody formation [1620]; pyridoxine may be a factor essential for the maintenance of lymphoid tissue. Rats and rabbits deficient in vitamin-B complex or in vitamin A were capable of producing antibodies in amounts equal to those produced by animals receiving these vitamins [1621].

A recent editorial in the *Journal of the American Medical Association* (466, **137**, 1948) points out that the effect of a vitamin deficiency on the resistance to infection would appear to depend upon the relative requirements of the infectious agent and of the host for the particular vitamin. Should the invading organism require larger amounts of the vitamin than the host, a deficiency of the vitamin would be expected to increase the resistance to the infection. If the opposite holds true then the vitamin deficiency will result in a decrease of the resistance of the host.

Para-aminobenzoic acid has been successfully employed in the treatment of rickettsial infections. Snyder *et al.* [1622] demonstrated a reduction of mortality rate following the oral administration of this substance in experimental murine typhus in mice. Hamilton *et al.* [1623] showed the inhibiting properties of the vitamin in the growth of epidemic and murine typhus rickettsias in chick embryos. These results were confirmed by an investigation of Grieff *et al.* [1624]. Zarafonetis and his colleagues [1625] were unable to demonstrate any apparent disturbance of antibody dynamics in clinical cases treated with para-aminobenzoic acid; they consider that the multiplication of rickettsial organisms within the cells is inhibited, thus allowing the immunity mechanisms of the body to dispose of them. No direct lethal action is exerted on the rickettsias by para-aminobenzoic acid.

The concentration of para-aminobenzoic acid in the system is not necessarily a measure of its efficacy. Parenteral administration or forced feeding of para-aminobenzoic acid thrice daily was ineffective in influencing the course of spotted-fever infection

in guinea-pigs, although high blood levels were produced; in contrast, addition of 1 to 2 per cent of para-aminobenzoic acid powder to the diet of the guinea-pigs allowed of an almost continuous intake of the compound and proved effective in treatment [1626].

Para-aminobenzoic acid was found to be efficacious in the therapy of clinical louse-born typhus [1627]. A case of Rocky Mountain fever responded to this form of treatment [1628]. Tierney [1629] treated 18 cases of tsutsugamushi fever (scrub typhus) and concluded that para-aminobenzoic acid administered during the first week of the disease is an effective therapeutic agent. A possible complication is the fall in the white cell count and Tierney recommends discontinuation of treatment when the total white cell count has decreased below 3,000 per c.mm. or the granulocytes have become less than 30 per cent of the total white count. Tierney also observed a more abrupt therapeutic response from a high blood level of the vitamin, but this tended to promote mental confusion; blood levels of 30 to 60 mg. per 100 c c. were not associated with mental reaction Acidosis, leucopenia, abdominal distension and delirium are the possible toxic effects of this method of treatment according to Ravenel [1630], he prescribed para-aminobenzoic acid in Rocky Mountain spotted fever with excellent results. Ravenel recommends doses of 0·5 to 1 gram per pound of body-weight per day at two-hourly intervals; the compound should be buffered with 10 c c. of 5 per cent solution of sodium bicarbonate per gram. Blood levels greater than 80 mg. per 100 c.c. are dangerous. Ten cases of Rocky Mountain spotted fever were successfully treated with para-aminobenzoic acid and it was suggested that the optimum level of the compound in the blood is 30 to 60 mg. per 100 c.c. [1631].

Vitamin C

Infection increases the demands for vitamin C. Scorbutic guinea-pigs are less resistant to infection, but no diminution in the antibody content of the blood was observed in such animals [1632, 1633] Perla and Marmorsten [1634] concluded that vitamin C had no relation to the production of natural or of immune antibodies. While *in vitro* experiments have demonstrated a bactericidal action for vitamin C, it has been shown that the amount of ascorbic acid normally present in human blood is incapable of exerting a similar activity [1635]. Ecker *et al.* [1636] suggested a correlation between the serum complement and vitamin C in human beings, but Kodicek *et al.* [1637] refuted this claim. Crandon *et al.* [1639] found no reduction of the complement in the presence of established

scurvy in man. Spink *et al.* [1638] were unable to demonstrate any relationship between the bactericidal activity of human serum and vitamin-C content. The nature of the decreased resistance of scorbutics to infection is suggested by Ralli and Sherry [1642] to depend on the fact that some relationship exists between the presence of normal intercellular material and the maintenance of the natural resistance of the organism. A neutralizing action of vitamin C on diphtheria toxins was recorded by Harde [1640] and since then there have been conflicting reports regarding the authenticity of this activity in man. Meyer and Meyer [1641] consider that vitamin C is essential for normal local reaction to inflammatory agencies; fibroblastic formation suffers in avitaminosis C. The viricidal action of ascorbic acid is thought to be due in large part at least to the production of hydrogen peroxide.

Feller *et al.* [1643] obtained negative results regarding the ability of vitamins A or C to influence the capacity of nasal secretions to inactivate virus; these vitamins exerted no apparent influence on the activity of lysozyme in the nasal secretions, the titre of complement in the blood serum or on the phagocytic activity of neutrophils for pneumococci. A supplement of vitamin C given to over 300 boys between the ages of 15 and 20 had no influence in reducing the incidence or duration of colds [1644]. Brown *et al.* [1645] found that the administration of 1 gram of ascorbic acid on each of two successive days produced a statistically significant reduction in the duration of the common cold. On the other hand Dahlberg *et al.* [1646] observed no beneficial response on the incidence or duration of colds from the administration of 50 mg. of vitamin C daily for three months. From a study of the effect of vitamin C on whooping cough, Gardiner [1647] concluded that ascorbic-acid therapy in no way alters the course of the disorder.

The increased requirements of vitamin C in malaria necessitates its administration in the acute phase of the disorder to prevent a mild state of scurvy [1648]. Monkeys deficient in vitamin C show an abnormal course of the parasitaemia following inoculation of *P. knowlesi*.

Tuberculosis in the active state is associated with heightened demands for ascorbic acid, but there is no definite evidence to show that, when these demands are met, increased allowances exert a beneficial effect upon the healing of the lesions. Similarly in syphilitic infections vitamin C plays no significant rôle beyond perhaps acting as a detoxifying agent to arsenic and bismuth. However, Ruskin [1649] claims that ascorbic acid enhances the therapeutic activity of bismuth. Vitamin C does not influence the Wassermann reaction in syphilitic subjects.

Vitamin D

Although cod-liver oil has been prescribed for many years for patients with pulmonary tuberculosis, there is little to suggest that vitamins D or A have any specific influence on the disease. Calcification will occur only when the lesion has healed and is not hastened by vitamin-D therapy. However, Raab [1650] describes experiments which are stated to demonstrate a bactericidal action of vitamin D on the tubercle bacillus, *in vitro* and *in vivo*. Wallace [1651] reports good results in some patients suffering from tuberculous glands with sinuses following treatment with calciferol in high dosage. No improvement in the condition of pulmonary tuberculosis succeeded massive vitamin-D administration [1652]. While a favourable reaction of non-pulmonary tuberculosis may sometimes be obtained with massive vitamin-D therapy, disadvantages are the occasional dissemination of tuberculosis in the flare-up of a quiescent lesion elsewhere [1653]. Existing pulmonary tuberculosis may be greatly aggravated during massive vitamin-D therapy.

Vitamin K

A number of reports exist indicating the frequency of hypoprothrombinaemia in tuberculous patients Vitamin-K therapy restores the prothrombin level to normal values, but only so long as the vitamin is being administered [1654]. This medication is without effect on complicating haemorrhage [1655]. Bleeding may appear even when vitamin K has been administered over a long period. The origin of the low blood prothrombin levels would appear to be related to toxaemia and hepatic damage.

Two cases of leprosy were treated with calciferol by Chaglassian (*J. Invest. Dermatol.* (1948) **10**, 303) with marked improvement.

SULPHONAMIDES AND VITAMINS

Antibacterial Action of Sulphonamides

AMONG THE theories propounded in explanation of the antibacterial action of sulphonamides is the view that inhibitors of bacterial growth act by interference with metabolites essential for normal growth of micro-organisms. Fildes [1656] suggested that para-aminobenzoic acid, normally associated with an enzyme system, is an essential metabolite for organismal growth and that the effects of sulphonamides are attributable to interference with the metabolism of this substance. Woods [1657] considered that sulphanilamide competes with para-aminobenzoic acid, by virtue of its similarity in structure, for enzymes whose functioning is necessary for the growth of bacteria. Landy and Wyeno [1658] demonstrated the neutralizing effects of para-aminobenzoic acid, when added to culture media, on the action of sulphonamide, sulphapyridine and sulphathiazole on streptococci, pneumococci and staphylococci. According to Sevag [1659] the inhibition of sulphonamides by para-aminobenzoic acid is a non-specific effect, comparable to the non-specific antagonism shown by urethane, guanine, xanthine, etc. Sulphonamides may enter into a reversible combination with the specific proteins of bacterial respiratory enzymes, and so inhibit the growth of bacteria. Co-enzymes which are derivatives of certain vitamins also form reversible combinations with these same enzyme proteins, and there is consequently an antagonism between certain vitamins and sulphonamides; the result of this antagonism is dependent on the concentration and relative degree of affinity of the competing substances for the enzyme protein [1659].

Sevag quotes the findings of certain experiments in which nicotinamide, thiamine, cocarboxylase, riboflavin or pantothenic acid have completely counteracted the sulphonamide effect. The Fildes-Wood theory is probably too simple an explanation and direct proof of it is not available. Much work remains to be done to elucidate the mechanism of action of the sulphonamides. The latter may possibly inhibit a phase of respiration which provides the energy for bacterial division [1660] or may interfere with the synthesis of tryptophane from amino-acids and glucose [1661].

Sulphonamides and Local Anaesthetics

Procaine (novocaine), an ester of para-aminobenzoic acid, is

beta-dimethylaminoethyl-p-aminobenzoate. It can be hydrolysed in the body by esterases with the liberation of para-aminobenzoic acid [1662]. Woods [1657] demonstrated that procaine exerted a marked inhibitory effect on the bacteriostatic action of sulphonamides *in vitro*, and Walker and Derow [1663] found that this effect was exactly comparable with that of para-aminobenzoic acid, mol for mol. Local infiltration with small amounts are adequate to prevent the action of sulphonamides applied topically in the treatment of wound infection; it was concluded that procaine in quantities ordinarily employed for local anaesthesia may be absorbed into the circulation in amounts adequate to exert an inhibitory effect on the sulphonamide drugs present in the blood [1664]. The suggestion was made that under such circumstances, when the use of local anaesthesia is necessary, derivatives of para-aminobenzoic acid should be avoided. No appreciable quantities of para-aminobenzoic acid accumulate in the blood following spinal anaesthesia [1665].

Para-aminobenzoic acid, given orally, is rapidly excreted in the urine, chiefly in the conjugated form [1666] and accordingly its oral administration would not seem to be contra-indicated when sulphonamide therapy is prescribed simultaneously [1667]. Only a partial prevention of the action of succinylsulphathiazole is exerted by para-aminobenzoic acid [1668]. One interpretation of sulphonamide-fastness is that the organism in question develops the ability to synthesize para-aminobenzoic acid in excess of normal metabolic requirements as a consequence of long exposure to sulphonamide drugs. Resistant strains of *Staphylococcus aureus* are said to produce seventy times more para-aminobenzoic acid than do parent strains of the same micro-organism [1669] and Landy *et al.* [1670] found that resistant bacteria synthesize 100 times more para-aminobenzoic acid than the average production of twenty different bacterial genera. Para-aminobenzoic acid has a pronounced anti-promin effect on the growth of tubercle bacilli [1671]. The difficulty of obtaining positive cultures in specimens removed from a subject undergoing treatment with sulphonamides may be overcome by the addition of para-aminobenzoic acid which will counteract the sulphonamide contained in the specimen.

Toxic Effects of Sulphonamide Therapy

Sulphaguanidine and succinylsulphathiazole have been widely used in animal experiments as a means of producing vitamin-deficiency states. Their action would appear to depend on an alteration of the intestinal flora, the sulphonamide compounds affecting primarily the vitamin synthesizers (i.e. coliform organisms)

and not the vitamin requirers (i.e. lactobacilli, streptococci and anaerobic bacteria) [1672]. The number of *E. coli* organisms is depressed in the faeces but the total organismal count remains unaffected. Deficiency syndromes of nicotinic acid, vitamin K, biotin, pantothenic acid, inositol and folic acid have been produced experimentally by the oral administration of these sulphonamide drugs evidently because of their interference with normal biosynthesis of the vitamins. An interesting possibility has been raised that tolerance to the sulphonamides may be related to the activities of the coliform organisms in the intestines.

Ahmed [1673] stresses the similarity of the toxic effects of sulphonamides and those of nicotinic-acid deficiency, and advocates treatment with 100 mg. of nicotinic acid ingested twenty minutes before a dose of the drug. Brown *et al.* [1674] found that nicotinic acid in 50 mg. doses reduced the nausea and vomiting encountered in sulphonamide therapy and Doughty [1675] claimed ameliorating effects on the toxic features by the use of 20–50 mg. nicotinic acid thrice daily. On the basis of experimental evidence, Gross *et al.* [1676] suggested that folic-acid concentrate, biotin and liver therapy might prove valuable in counteracting the toxic reactions of sulphonamides. There is some evidence that certain sulphonamides containing the pyridine ring, especially sulphapyridine, and nicotinic acid are mutually antagonistic – another instance of two substances of like chemical structure, competing for the same enzyme systems. This action may, besides that of interference with intestinal biosynthesis, promote the untoward effects witnessed in treatment with sulphonamides. Interference with the enzyme systems which are connected with carbohydrate metabolism may account for the mental derangement occasionally encountered. Accordingly a valuable prophylactic measure against the development of certain untoward sulphonamide reactions would appear to be the prescribing of adequate supplements of vitamin B.

Because of the production of polyneuritis following the use of sulphonamides, an interference with the metabolism of vitamin B_1 has been suggested, but Fleisch and de Preux [1677], from experiments in animals, concluded that toxicity of the sulphonamides could not be attributed to a state of vitamin-B_1 deficiency. Mouriquand *et al.* [1678] claim that an antagonism exists between ascorbic acid and the sulphonamides, and Holmes [1679] noted a marked increase in the urinary excretion of vitamin C following the administration of sulphonamide drugs; on the other hand Jones *et al.* [1680] did not find that the presence of sulphonamides affected the ascorbic-acid content of the wound, retard its healing or reduce the tensile strength of the scar. McCormick [1681] states that concurrent administration of large doses of vitamin C

not only prevents the toxicity of sulphonamides but also enhances their bacteriostatic activity.

Rats fed succinylsulphathiazole showed a marked reduction in the vitamin Bc potency of their livers [1682] and considerably less folic acid was recoverable from the faeces [1683]. Experimental neutropenia in animals following sulphonamide administration can be cured with folic acid. The influence of pyridoxine on the lowered white cell count consequent on sulphonamide therapy may be indicative of an interference with this vitamin.

In a series of 68 patients receiving sulphonamides for acute infective processes, there was a significant decrease in the prothrombin level during chemotherapy which was apparently attributable more to the severity of the infection than to the sulphonamides [1684]. Vitamin K has been suggested in the treatment of purpuric rashes arising during the course of sulphonamide administration. When a surgical operation is contemplated in a patient who is receiving sulphonamide therapy and in whom a hypoprothrombinaemia arises, vitamin K should be prescribed.

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ADDENDUM

[*Page 60*]

Experiments in animals have shown the necessity for the inclusion of adequate amounts of folic acid in the diet for the prevention of greying. A review of nutritional factors and greying is presented by Frost (*Physiol. Revs.* (1948) **28**, 368).

[*Page 65*]

Vitamin B12

From proteolysed ox liver, red amorphous materials were extracted and were found to be highly active in the treatment of pernicious anaemia (Rickes *et al.* (1948) *Nature*, **161**, 638). The clinical activity of the extracts was infinitely greater per unit of weight than liver extract, folic acid or thymine; 1 gram only was procured from 4 tons of liver. Following subsequent research the crystalline anti-pernicious anaemia factor – vitamin B12 – was isolated from the amorphous preparations. A similar line of investigations under Dr Lester Smith had proceeded in England. Clinical assay has hitherto been necessary for the standardization of the anti-pernicious anaemia potency of liver preparations, but Shorb (*Science* (1948) **107**, 397) demonstrated a factor in liver extracts necessary for the growth of *Lactobacillus lactis* Dorner and it is probable that this microbiological method may offer an accurate measure of the anti-anaemia factor Vitamin B12 contains cobalt and phosphorus (*Nutrition Revs.* (1948) **6**, 291). In ruminants, not infrequently an anaemia arises from naturally occurring dietary deficiencies of cobalt; the requirement of cobalt may be associated with vitamin B12 formation. Excess of this essential trace element in nonruminants may lead to polycythaemia.

Success with vitamin B12 has been reported in the treatment of pernicious anaemia. Two cases of nutritional tropical anaemia and one case of non-tropical sprue have been satisfactorily treated with vitamin B12 (*South. Med. J.* (1948) **41**, 522); provided the dosage is adequate the clinical and haematological features of sprue respond (*Blood* (1948) **3**, 1213) Ungley (*Lancet* (1948) **1**, 771), in a study of three patients with subacute combined degeneration, noted that the degree of improvement following injections of vitamin B12 was similar to that produced by crude liver extract; Berk *et al.* (*New Eng. J. Med.* (1948) **239**, 328) obtained corresponding results The mucous membrane lesions of pernicious anaemia also respond to the vitamin (*J. Lab. Clin. Med.* (1948) **33**, 1019). That vitamin B12 can resolve the neurological complications

tends to disprove the theory of a deficiency, distinct from that of the anaemia, as a cause of the neurological lesions and distinguishes it from the activities of folic acid. Liver sensitivity is attributable to a substance other than vitamin B12, since no untoward reaction attends its use in liver-sensitive subjects. Before true assessment of the value of vitamin B12 in the remission of all aspects of the syndrome of pernicious anaemia can be made, a sufficiently long period of observation is required.

[*Page 69*]

An experiment was conducted on 20 human volunteers (*Lancet* (1948) **1**, 853) who, following a preliminary period of saturation, were given a well-balanced diet, except that it contained less than 1 mg. of irremovable vitamin C. Ten were given no additional supply of ascorbic acid and all developed scurvy; it was found that 10 mg. of vitamin C daily sufficed to produce a steady improvement. While this affords reasonable evidence for considering that 10 to 11 mg. is the minimal daily requirement for the human adult, it was concluded that 30 mg. of the vitamin daily was a reasonable recommendation, since this dosage allowed a margin of safety for additional needs. The daily intake of 75 mg. recommended by the U.S. National Research Council would not appear to possess any advantage over the 30 mg. recommended by the League of Nations Technical Commission on Nutrition (*Brit. Med. J.* (1948) **2**, 828).

[*Page 87*]

The biochemical findings in calciferol toxicity are: a rise in total serum calcium, a rise in diffusible serum calcium (normal $5{\cdot}4 \pm 0{\cdot}1$ mg. per cent), no alteration of the ionic fraction of serum calcium, a rise in serum proteins and evidence of renal involvement (*Brit. J. Dermat. Syph.* (1948) **60**, 164). The degree of permanency of the renal damage is not yet apparent but was found to be greater in adults and the rate of recovery to be greater in children (*Brit. Med. J.* (1948) **1**, 430).

[*Page 170*]

An important contribution to our knowledge of kwashiorkor has been made by Davies (*Lancet* (1948) **7**, 317). The primary factor in pathogenesis is a pancreatic disturbance due to malnutrition and possibly intensified by malaria. Pathological changes are found in the pancreas. As a consequence of the pancreatic dysfunction fatty infiltration of the liver with subsequent fibrosis ensues; pancreatectomy in the dog kept alive with diet and insulin is succeeded by hepatic fatty infiltration. This view is supported by Davies's observation of the occurrence of diabetic and hypogly-

caemic coma in kwashiorkor. Hepatic cirrhosis is a late manifestation of the disorder, as are pancreatic fibrosis and a form of nephritis. Holmes and Trowell (*Lancet* (1948) **1**, 395) observed that, in malignant malnutrition in Uganda, there is a failure of the liver cells to store glycogen even when abundant glucose is given intravenously. The liver cells, however, are not glycogen-free and appear capable of synthesizing glycogen, although apparently not from glucose; the liver cells are also capable of mobilizing glycogen.

[*Page 201*]

Since the above discussion of the sprue syndrome was originally written, reports have appeared in the literature which would seem to invalidate some of the statements made. Reviewing this subject Davidson (*Edin. Med. Jour.* (1948) **55**, 400) points out that, while tropical sprue, idiopathic steatorrhoea and coeliac disease present identical clinical, biochemical and radiological features, the response to folic-acid therapy is variable in the three groups and in individual members of the same group. When the anaemia is megaloblastic in type, a clinical and haematological response can be expected following treatment with folic acid Should the anaemia be normoblastic in type, the intestinal features and the fat absorption defect may respond while the anaemia remains uninfluenced. Some examples of the sprue syndrome fail to show any response to folic acid; this occurs especially when the anaemia is of the normoblastic variety. Reports from America on the use of folic acid in coeliac disease have not been encouraging. Davidson states that, in coeliac disease associated with a megaloblastic anaemia, improvement in all respects ensues with folic-acid treatment; the anaemia in coeliac disease is usually normoblastic in type, but Davidson advises that this form of therapy be tried in every case of the sprue syndrome, even when normoblastic anaemia exists, the treatment being abandoned after fourteen days if no improvement results

[*Page 227*]

Interest has recently been focused on substances which are variants of the folic-acid molecule and on folic-acid antagonists Of the former, two examples are diopterin (pteroyldiglutamic acid) and teropterin (pteroyltriglutamic acid). Dodds (*Lancet* (1948) **2**, 837) briefly reviewed the present position of this work. Results with teropterin have been more promising than with diopterin and claims are advanced that teropterin produces considerable recovery in the health of patients suffering from malignant disease and, in some instances, affects the growth of the tumour. These claims have been challenged and Dodds obtained the impression

that in the United States enthusiasm for the use of teropterin was waning. Since folic acid is essential for the growth of cells, and since malignant cells are more susceptible to deprivation of folic acid, the use of folic-acid antagonists in patients with malignant disease has seemed a valuable procedure. Aminopterin (4-aminopteroylglutamic acid) is a folic-acid antagonist, but therapeutic dosage approximates to the toxic dose. An important feature of aminopterin is its anti-oestrogenic action Dodds also refers to A-methopterin, which appears to possess all the properties of *aminopterin while having but one-tenth of its toxicity.*

Following the demonstration of an 'acceleration phenomenon' in acute leukaemia of children treated with injections of teropterin and diopterin, Farber *et al.* (*New Eng. J. Med.* (1948) **238**, 787) employed aminopterin in the therapy of this disorder and obtained temporary remissions; there was no evidence of actual cure and the toxicity of the compound was stressed The writer of an editorial in *Blood* (1948, **3**, 1057) states that, from personal communications from various centres, aminopterin and allied drugs have proved disappointing in leukaemia. Complications, such as haemorrhage, aplastic anaemia and severe reactions of the mucous membranes, were common; he himself, however, was impressed with the results of his own and Farber's experiences, in both of which the *factor of spontaneous remission could be excluded.*

[*Page 239*]

Not only does folic acid fail to prevent the neurological complications in pernicious anaemia, but evidence exists that the vitamin may itself be responsible for the appearance of the nervous lesions. The acute onset of the neurological syndrome in such treated cases is quite unlike that encountered in those inadequately treated with liver. A further point of distinction is the rapidity with which the neurological manifestations during folic-acid therapy yield to treatment with liver. The concurrent administration of folic acid and liver may prevent the resolution of the neurological disorder. Meyer (*Am. J. Clin. Path* (1948) **18**, 811) reports a case of macrocytic hyperchromic anaemia *attributable to intestinal* absorptive defect; sensitivity to liver developed, and after thirteen months of folic-acid therapy neurological lesions appeared; *desensitization to* liver was effected and with subsequent liver therapy complete neurological remission ensued. Also disturbing is the report of Davidson and Girdwood (*Lancet* (1948) **1**, 360); in two cases of steatorrhoea severe polyneuritis developed during treatment with folic acid. The latter investigators suggest a vitamin imbalance as the cause. Folic acid may by some antagonistic action augment a latent state of vitamin deficiency. Ross *et al.* (*Blood*

(1948) 3, 68) ...
larger doses o ...
folic acid ma' ...
acid; folic acid has glutamic acid as a terminal group. Thymine neither prevents the onset of, nor cures, subacute combined degeneration of the cord (*Am. J. Med. Sc.* (1948) **216**, 270).

[*Page 261*]

In an experiment on human volunteers (*Lancet* (1948) **1**, 853) who consumed a diet containing less than 1 mg. of irremovable vitamin C, 10 of the subjects who received no additional supplies of the vitamin developed scurvy. Of these 10, one developed an acute cardiac disorder, the electrocardiogram revealing features suggestive of coronary thrombosis. Another subject experienced praecordial pain and the electrocardiogram demonstrated a partial heart-block. Much anxiety was aroused by the condition of the individual with the former cardiac affection and accordingly it is evident that any patient suffering from scurvy should be admitted to hospital and saturated with ascorbic acid as soon as possible (*Brit. med. Jour.* (1948) **2**, 828).

[*Page 267*]

Further clinical investigations of the value of vitamin E in cardiac disease have produced conflicting results. Vogelsang *et al.* (*Med. Rec.* (1948) **161**, 83) have treated 1,500 cases of all types of cardiac disease and concluded that 80 per cent of cases showed continuous improvement. The basis of this improvement is ascribed to the action of vitamin E in reducing the permeability of the capillaries, while dilating these vessels; it is also maintained that thrombus formation is prevented, that formed thrombi are resolved and that vascularization of scar tissue is promoted. It will be recalled that Mason ascribed the effects of vitamin-E deprivation in the rat to changes in the vascular system. Vogelsang *et al.* claim good results from vitamin-E therapy in vascular abnormalities, such as venous thrombosis, cerebral thrombosis, thrombo-angiitis obliterans, arteriosclerotic gangrene and chronic ulceration. The dosage recommended is 200 mg. daily, although in the preliminary period of treatment as much as 900 mg. may be prescribed; the latter dosage is contra-indicated in the presence of chronic rheumatic disease and advanced hypertension. Levy and Boas (*Ann. Int. Med.* (1948) **28**, 1117) obtained no satisfactory results with a dosage of 200 to 800 mg. of vitamin E daily over several weeks, in angina pectoris, coronary thrombosis or chronic rheumatic endocarditis. Similarly, Markinson and his colleagues (*Lancet* (1948) **1**, 102) found vitamin E to be ineffective in angina

pectoris. Baer *et al.* (*Am. J. Med. Sc.* (1948) **215**, 542) reported no significant improvement and no alteration in the electrocardiogram, orthodiagram or blood pressure in 11 patients with congestive heart disease, 5 patients with angina pectoris and 6 patients with hypertension, following treatment with 300 to 400 mg. vitamin E daily.

Vitamin P

[*Page 275*]

Rutin, which is allied to vitamin P, has been used in a variety of disorders which are characterized by increased capillary fragility, such as hereditary haemorrhagic telangiectasia, idiopathic pulmonary haemorrhage and the decreased capillary resistance of hypertension. Conflicting results have been recorded. A greater incidence of increased capillary fragility was observed in diabetic subjects as compared with non-diabetics and diminution of capillary resistance was a frequent concomitant of diabetic retinopathy. Accordingly rutin has been used for the latter condition. Levitt *et al.* (*Am. J. Med. Sc.* (1948) **215**, 130) treated 12 patients with diabetic retinal haemorrhages, associated with increased capillary fragility, with rutin, but were unable to attribute improvement to the treatment; diabetic retinitis progressed rapidly in one patient while under treatment. Rodriguez and Root (*New Eng. J. Med.* (1948) **238**, 391) from a study of 150 patients, concluded that while the capillary fragility may be restored to normal in diabetic subjects by prolonged administration of rutin, no change in the retinitis can be anticipated. Solloff and Bello (*Am. J. Med. Sc.* (1948) **215**, 655) were unable to find any correlation between retinal haemorrhages and a positive Rumpel-Leede test. It would not appear that rutin is of much, if any, therapeutic benefit to diabetic patients, although it may possess activity in decreasing the capillary fragility as measured by the positive pressure method (*Nutrition Revs.* (1948) **6**, 301).

Rutin may restore the increased capillary fragility of hypertensive subjects to normal and is a valuable agent in the prevention of the increased capillary fragility encountered during thiocyanate therapy for hypertension. However, subconjunctival haemorrhage may occur in patients with hypertension while receiving rutin; the capillary fragility was normal in two such patients at the time of appearance of the haemorrhage (*J. Am. Med. Assoc.* (1947) **134**, 692).

[*Page 280*]

The unsatisfactory position of the treatment of chilblains is testified by the numerous preparations advocated. In this respect vitamins have extensively been used. Nicotinamide and nicotinic

acid have been mentioned. Calciferol has also been recommended, and with it calcium has been prescribed. The claims for its efficacy have been many, but Anning (*Lancet* (1947) **2**, 794) was unable to discover any value of calciferol either in the prevention or treatment of chilblains. Similarly vitamin K has been reported to be successful in relieving chilblains, but again negative results have been obtained by other investigators. It is pointed out that where adequate central heating exists chilblains clear up. In spite of very cold weather, the condition is non-existent in many areas of Canada and the United States (*Lancet* (1947) **1**, 160).

[*Page 283*]

Some 60 per cent of cases of lupus vulgaris may be cured by calciferol; calciferol, added to the medium in concentrations up to 500 units per ml., was without effect on the morphology or pathogenicity of the tubercle bacillus (*Brit. Med. J.* (1948) **1**, 386). Dowling *et al.* (*Brit. Med J* (1948) **1**, 430) emphasise that local treatment greatly accelerates healing during calciferol administration; they stress the significance of a rise in the blood sedimentation rate and, in children, a rise in the blood urea as indications of toxic effects. Tomlinson (*Lancet* (1948) **1**, 327) investigated the calcium content of the skin in cases of lupus vulgaris treated with calciferol. He observed that healed lupus skin contained a higher calcium content than normal skin removed from non-lupus patients who had not received calciferol, and that healed lupus skin had a higher calcium content than non-lupus skin taken from the same patient at the same time; he suggested that calciferol makes calcium available to lupus tissue Charpy and Pichat (*C.R. Soc. Biol , Paris* [illegible] **111**, [illegible]

[illegible]

stances are given concurrently.

[*Page 286*]

Recent work on vitamin E in the treatment of the collagenoses, such as atopic dermatitis, granulomatous ulcer of the leg, sclerosis of the leg and lupus erythematosus, has been reported by Burgess (*Lancet* (1948) **2**, 215). In several cases of atopic dermatitis, sebaceous secretion increased, comedones and dilated follicles appeared and a seborrhoeic dermatitis of the scalp was a feature. A favourable response was obtained in a long-standing case of granulomatous ulcer of the leg, the diagnosis being compatible with necrobiosis diabeticorum lipoidica. Favourable results in lupus erythematosus and in sclerosis of the leg associated with ulcers were

also procured. A varied, but in the main favourable response to tocopherol therapy was found in other collagenoses – dermatomyositis, lichen sclerosis et atrophicus, scleroderma, morphea and granuloma annulare. Burgess considers that vitamin E may exert a profound influence on enzymatic reactions within the cells. He emphasizes that continued treatment is necessary to prevent relapse. The daily doses used were 100 to 600 mg. Shute *et al.* (*Surg. Gynec. Obstet.* (1948) **86**, 1) also record the satisfactory treatment of leg ulcers with vitamin E.

INDEX